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NORTH AMERICAN BLASTOMYCOSIS (GILCHRIST'S DISEASE)

I A Study of the Disease from a Review of the Literature

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WITH the exception of actinomycosis, systemic mycotic infections have been rarely reported from Canada. The ease with which such diseases may be misdiagnosed, as occurred in the case to be reported in a subsequent publication, would appear to be sufficient justification for presenting a review of the subject of blastomycosis.

DEFINITION OF FUNGI

Lewis and Hopper¹ gave the following description:

Fungi are microscopic members of the plant kingdom. They are included in the phylum of Thallophyta, in which there is no differentiation into roots, stem and leaves. Structurally, they consist of vegetative elements and of fructification, or spore, forms. The vegetative filamentous structures are irregularly segmented and show some variation in form, according to the species. This is the form in which fungi are chiefly present in the human body. The structures connected with fructification are more specific, forming the basis for the identification of species. They are rarely present except in artificial cultures.

HISTORICAL DATA

In 1894 Gilchrist and Stokes² presented a clinical description of the cutaneous type of blastomycosis as it appeared in the United States and at the same time identified the causative fungus in stained tissue sections. In 1898 Gilchrist gave the organism the name by which it is still recognized, *Blastomyces dermatitidis*. In 1902 the first case of the systemic disease was reported by Walker and Montgomery. Since that time the disease has been called by many names, but only three of these are now acceptable—blastomycosis, North American blastomycosis and Gilchrist's disease. Confusion has existed in the literature, owing to

From the Department of Medicine, Ottawa Civic Hospital

1 Lewis, G M, and Hopper, M E. An Introduction to Medical Mycology, ed 2, Chicago, The Year Book Publishers, Inc, 1943, pp 5, 184-188 and 306-308.

2 Gilchrist, T C, and Stokes, W R. A Case of Pseudo-Lupus Vulgaris Caused by *Blastomyces*, J Exper Med 3 53, 1898.

the fact that infections caused by various fungi, somewhat similar morphologically, have all been termed blastomycosis

Conant and his co-workers³ wrote

The generic name *Blastomyces* is admittedly an unfortunate one. It had been used previously for an entirely different fungus and, according to the rules of nomenclature, it should be restricted to its first use. Also, the term means "budding," which is a phenomenon not only of the tissue phase of the etiologic agent of Gilchrist's disease, but also of fungi belonging to the genera *Saccharomyces*, *Cryptococcus* and *Candida*.

The European type of blastomycosis is a distinct entity and is known as cryptococcosis, torulosis or Busse-Buschke's disease, it is caused by a fungus of the genus *Cryptococcus*. The South American variety is often termed paracoccidioidal granuloma or Lutz-Splendore-De Almeida's disease, its organism is named *Blastomyces brasiliensis* or *Paracoccidioides brasiliensis*. Conant and Howell⁴ in 1942 published an interesting comparative study of the fungi of South American and North American blastomycosis. Still another source of confusion in the nomenclature concerns the strictly cutaneous disease known as chromoblastomycosis, due to still another type of fungus, which, however, does not reproduce by budding. The first Canadian report of this infection⁵ was published in 1945. All of these diseases are listed in the *Quarterly Cumulative Index Medicus* under the heading of blastomycosis. To clarify the confusion that still exists in the literature it would seem essential to identify all cases of infection by *B. dermatitidis* as North American blastomycosis or Gilchrist's disease.

Since Gilchrist's original report, many other workers have added to the knowledge of the disease, but none has contributed more outstanding studies than the Duke Medical School group headed by Martin and Smith. They have done a great deal to establish some semblance of order out of the chaotic confusion which previously existed.

DEFINITION OF GILCHRIST'S DISEASE

North American blastomycosis is a chronic infection, caused by *B. dermatitidis* and characterized by the formation of suppurative and granulomatous lesions in any part of the body, but with a predilection for the skin, lungs and bones.³

3 Conant, N. F., Martin, D. S., Smith, D. T., Baker, R. D., and Callaway, J. L. *Manual of Clinical Mycology*, National Research Council, Division of Medical Sciences (Military Medical Manual), Philadelphia, W. B. Saunders Company, 1944, pp. 25-50.

4 Conant, N. F., and Howell, A., Jr. Similarity of Fungi Causing South American Blastomycosis (*Paracoccidioidal Granuloma*) and North American Blastomycosis (Gilchrist's Disease), *J. Invest. Dermat.* 5: 353, 1942.

5 Berger, L., Beaudry, M., and Gaumond, E. Chromoblastomycosis Due to a New Species of Fungus (First Canadian Case), *Canad. M. A. J.* 53: 138, 1945.

Martin and Smith⁶ stated that two clinical types of Gilchrist's disease are recognized—a cutaneous type, which proceeds as a chronic or sub-acute ulcerating process and which usually responds in some degree to treatment with iodides or roentgen irradiation, and a systemic type, a highly fatal disease, characterized by pulmonary infection and widespread distribution of lesions in the subcutaneous tissues, bones, joints, internal organs and central nervous system. The same fungus, *B. dermatitidis*, causes both varieties.

GEOGRAPHIC DISTRIBUTION

In 1939 Martin and Smith⁷ reported a study of 347 cases of the disease. They considered only 80 (23 per cent) of these cases as having been unquestionably proved cases of infection by *B. dermatitidis*, but 163 (47 per cent) were classified as presumptive cases, on the basis of clinical histories, descriptions of the lesions, photographs, biopsies or positive smears. They dismissed 104 cases, because the descriptions were inadequate to allow inclusion in either of the categories. Cases in which the disease was reported as blastomycosis but in which it was obviously due to fungi other than Gilchrist's organism were not included in the statistical study.

They concluded that Gilchrist's disease is an infection essentially limited to North America, but found analysis of foreign reports of cases complicated by the failure to distinguish clearly between the American type caused by the moldlike *B. dermatitidis* and the European type caused by the yeastlike *cryptococcus*. Ninety per cent of all cases, 95 per cent of the proved and presumptive cases and 98 per cent of the proved cases originated within the United States. The disease has been reported from at least twenty-eight widely separated states, with the largest numbers from Illinois and Louisiana. In 1946 Friedman and Signorelli,⁸ in commenting on this statistical study, stated that the only 2 cases accepted as proved or presumptive which originated outside the United States were from England and Canada. These authors reported that the recent literature contained 1 additional case from England and 1 from Australia.

6 Martin, D. S., and Smith, D. T. Blastomycosis (American Blastomycosis, Gilchrist's Disease) II. A Report of Thirteen New Cases, *Am. Rev. Tuberc.* **39**:488, 1939.

7 Martin, D. S., and Smith, D. T. Blastomycosis (American Blastomycosis, Gilchrist's Disease) I. A Review of the Literature, *Am. Rev. Tuberc.* **39**:275, 1939.

8 Friedman, L. L., and Signorelli, J. J. Blastomycosis. A Brief Review of the Literature and a Report of a Case Involving the Meninges, *Ann. Int. Med.* **24**:385, 1946.

SEX AND AGE INCIDENCE

Martin and Smith⁷ confirmed previous reports that the disease is much more common in male patients, the ratio being 9 to 1. Fifty per cent of the patients were over 40 years of age, with almost as many between 20 and 40 years. However, no age group was observed to be immune.

INCIDENCE OF DISSEMINATION

In 1944 Fishman⁹ declared that since the disease was described in 1894 approximately 380 cases had been reported and that his review of the literature indicated that in only 73 of these was the disease definitely of the systemic variety. This is in contrast with D'Aunoy and Beven's¹⁰ earlier estimate that the disease in 40 to 50 per cent of all cases of Gilchrist's disease is systemic.

Solway and his co-workers¹¹ claimed that the cutaneous form of the disease rarely becomes disseminated and quoted Stober's¹² conclusion that of 29 cases of the systemic disease in only 3 cases did the disease result from a primary cutaneous lesion. They suggested that trauma, including surgical cauterization, might precipitate dissemination. It seems accepted that it is much more common for the systemic variety to have cutaneous manifestations than it is for the cutaneous type to become disseminated.

SOURCE OF THE ORGANISM

The fungus may have a saprophytic existence on plants, since numerous strains of blastomyces are widespread in nature.¹ Its natural habitat is dark moist filthy unventilated ground, and, therefore, stables, cellars and other unhygienic places provide the proper environment for infection.¹¹ It most commonly infects agricultural workers, common laborers and persons who work or live in damp, dirty or wooded places.

PORTAL OF ENTRY AND MODE OF TRANSMISSION

Although the exact method of infection is not yet clearly understood, it is generally agreed that the organism enters the body either by way of the respiratory tract, from inhalation, or through an abraded

⁹ Fishman, J. Systemic Blastomycosis, with a New Form of Therapy, *U S Nav M Bull* 43 758, 1944.

¹⁰ D'Aunoy, R., and Beven, J. L. Systemic Blastomycosis, *J Lab & Clin Med* 16 124, 1930.

¹¹ Solway, L. J., Kohan, M., and Pritzker, H. G. A Case of Disseminated Blastomycosis, *Canad MAJ* 41 331, 1939.

¹² Stober, A. M. Systemic Blastomycosis. A Report of Its Pathological, Bacteriological and Clinical Features, *Arch Int Med* 13 509 (April) 1914.

cutaneous area.⁸ The cutaneous variety commonly results from trauma, such as scratches, bruises or puncture wounds, which introduce foreign bodies, such as thistles, thorns and splinters of wood. Crich¹³ suggested that the disease in his case may have resulted from the patient's chewing grass. Beregoff-Gillow¹⁴ stated that the essential transmitters of the mycelia or spores of the fungi are food in disintegration, water and air, but occasionally they may be transmitted by mosquitoes, fleas and bed-bugs, however, other writers do not mention the possibility of insects as vectors.

Evans¹⁵ reported a case of direct transmission of the disease in a physician who injured his finger while performing an autopsy in a case of systemic blastomycosis, subsequently a cutaneous lesion developed at the site of the injury.

PERIOD OF INCUBATION

The period of incubation is usually stated to be unknown, but has been estimated as from one to two weeks.¹

DEMONSTRATION OF THE ORGANISM

The fungus may be identified in pus from cutaneous lesions or in sputum and occasionally even in urine and cerebrospinal fluid, but rarely in the blood. It is usually not difficult to demonstrate from the lesions in the skin, if one examines the pus from small abscesses at the periphery of a lesion. An unstained direct preparation, with or without the addition of 10 to 20 per cent sodium or potassium hydroxide to the material examined, will usually reveal the organism, if studied under the microscope with subdued light. Pus is expressed on a clean slide, and a cover slip is dropped on it. Budding cells should be readily observed, but, if they are not, the preparation may be ringed with petrolatum and left for a few hours, after which blastospores will probably be noted.

In stained specimens, the fungus is often missed, because of its close similarity to lymphocytes.¹¹ Fixed biopsy specimens may be stained with hematoxylin and eosin or phosphotungstic acid, but D'Aunoy and Beven¹⁰ expressed the belief that silver impregnation allows a better study of the causative organism.

¹³ Crich, A. Blastomycosis of the Gingiva and Jaw, *Canad. M. A. J.* **26** 662, 1932.

¹⁴ Beregoff-Gillow, P. The Importance of Early Diagnosis in Mycotic Diseases, with Special Reference to Blastomycosis, with a Brief Report of Two Cases, *Canad. M. A. J.* **34** 152, 1936.

¹⁵ Evans, H. A Clinical Report of a Case of Blastomycosis of the Skin from Accidental Inoculation, *J. A. M. A.* **40** 1772 (June 27) 1903.

While many writers have stated that it is often difficult to demonstrate the fungus in the sputum, Martin and Smith⁷ stated that its isolation is not difficult if sufficient material can be obtained

STRUCTURE OF THE FUNGUS

Microscopically, the organisms are seen as doubly refractile, often budding, round or oval cells, 8 to 20 microns in diameter. When a stained histologic section is examined, the characteristic budding thick-walled double-contoured fungi may be noted in giant cells or in granulation tissue.¹ An important feature is that in the tissues they multiply only by budding and form no mycelia or ascospores.¹¹

The morphologic picture varies even in the same strain, and occasionally different strains can be isolated from the same patient in separate lesions, but Martin's work has proved that these are all one and the same organism.⁸

CULTURAL CHARACTERISTICS

B. dermatitidis grows luxuriantly at room temperature on artificial mediums, but not so readily at higher temperatures or in the presence of bacteria and is therefore sometimes missed in incubated cultures.¹⁰ It is a nonfermenter.⁸ The procedures necessary for isolation and identification of the fungus can be summarized as follows.⁷ The material should be streaked heavily on blood agar plates and Sabouraud's slants. The blood agar is incubated at 37 C, while the dextrose agar is left at room temperature. The cultures should not be discarded for two or three weeks, since colonies of *blastomyces* may not appear for two weeks.

The organism on blood agar at 37 C grows as a small wrinkled waxy colony, not dissimilar to a colony of tubercle bacilli. Microscopically, it consists of large rounded thick-walled cells, many of them budding and some showing rudimentary hyphae⁷ (fig 1).

On Sabouraud's medium at room temperature, the fungus tends to remain yeastlike for only a short period of time, during which the mycelium is broad, thick-walled and closely septate, giving the general appearance of a geotrichum. Quickly the mycelial phase predominates, the culture developing a white cottony growth with an abundant aerial mycelium, which becomes tan to brown with age. Microscopically, this moldlike culture shows numerous oval to round conidia, 3 to 4 microns in diameter, attached to the hyphae near septations, other round to pyriform conidia, 4 to 5 microns in diameter, are borne on lateral sterigmata of varying lengths (fig 2). In old cultures many chlamydospores are developed, 7 to 18 microns in diameter, with outer

walls thickened to give unusual appearances. The mycelial phase can be converted to the yeastlike phase by subculturing the organism to fresh mediums and incubating at 37 C.

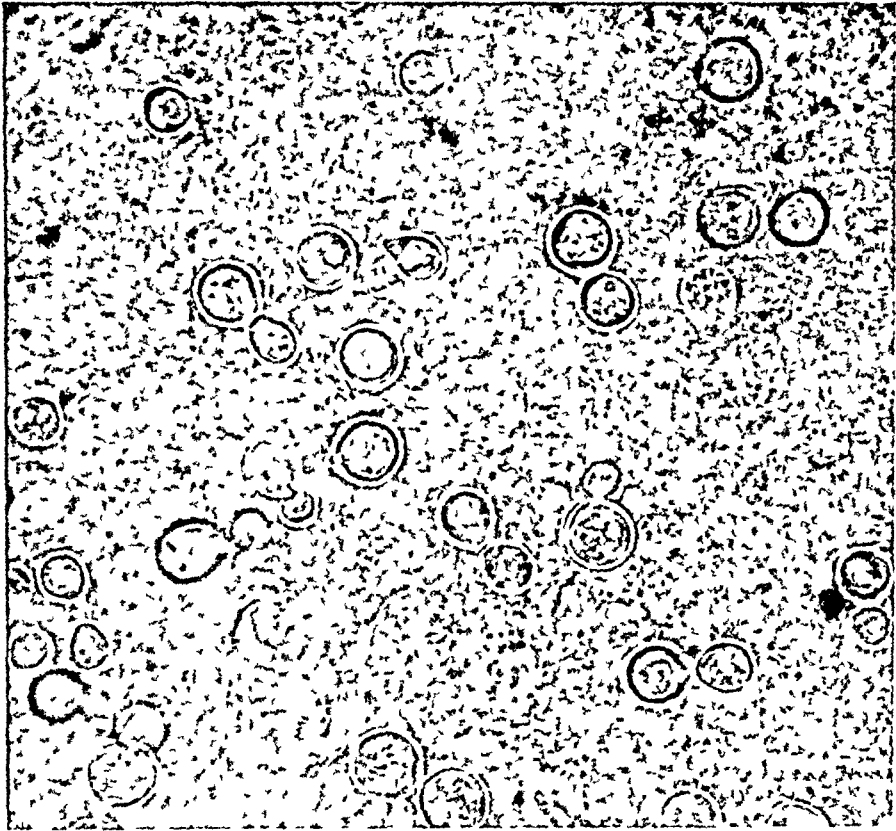


Fig 1—*Blastomyces dermatitidis*. Round double-contoured budding yeastlike cells in pus from a subcutaneous abscess ($\times 700$)

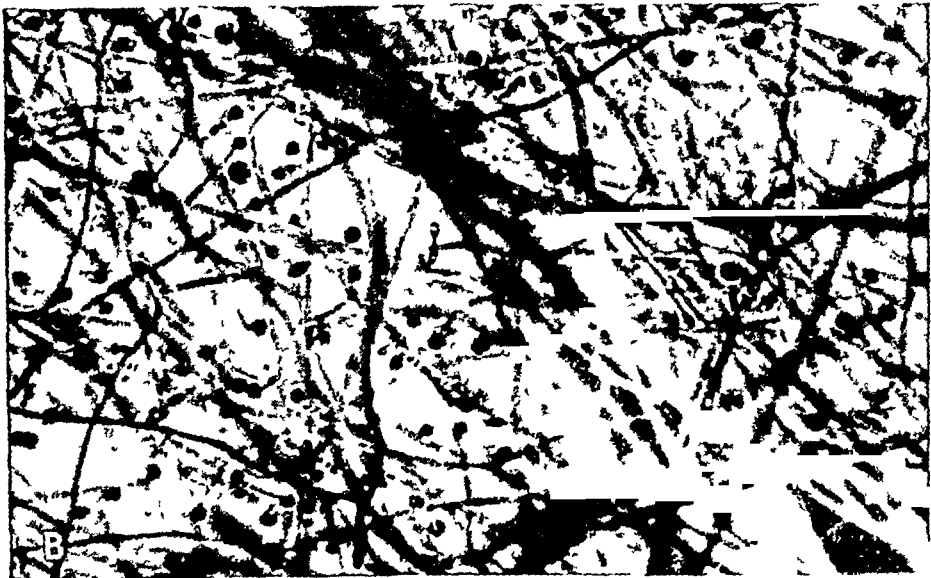


Fig 2—*Blastomyces dermatitidis*. Round and pyriform conidia seen in the filamentous stage from Sabouraud's glucose agar at room temperature ($\times 700$)

INOCULATION OF LABORATORY ANIMALS

The mouse is most susceptible, the rat is less so, and it is difficult to infect rabbits and guinea pigs. While the guinea pig dies of invasion when inoculated with *Coccidioides immitis*, it is commonly not infected by *B. dermatitidis*. Generalization of the infection, even in mice, does not always occur, and death of the animal should not be expected. Injection of infected material into the abdominal cavities of mice may allow recovery of the fungi from the peritoneal washings.¹¹

SYMPTOMS AND CLINICAL FEATURES

Cutaneous blastomycosis occurs most frequently on the face and other exposed areas of the body. It may be localized in one area or have a multiple distribution. On the face it commonly attacks the nose, lips, cheeks, forehead and eyelids, but spares the conjunctiva. The lesion first appears as a papular pustule, which soon ruptures, and a friable necrotic crust develops and slowly increases in size peripherally. The active margin of the lesion is typically violaceous and elevated $\frac{1}{8}$ to $\frac{3}{8}$ of an inch (about 0.32 to 0.96 cm) above the surrounding skin. The central area has a tendency to heal with fine soft scar formation, whereas the margin remains elevated and sharply demarcated from the surrounding normal skin. The crust is easily removed piecemeal, with little or no pain, and uncovers an almost flat bleeding base with papillary projections, which are bathed in serosanguineous exudate and pus. The peripheral area characteristically has numerous milium abscesses, which exude a thin purulent exudate on slight pressure. Material for smear, culture and biopsy should be obtained from this part of the lesion. The cutaneous lesions are either single or multiple, single lesions may reach a diameter of 8 to 10 inches (about 20 or 25 cm). Their shape varies greatly, but they are usually rounded, arciform or serpiginous in contour and are often confluent.⁸

In systemic blastomycosis there are no typical symptoms and signs, the disease being characterized by extremely protean manifestations. The onset is commonly insidious, and the symptoms at first may be those of a subacute infection of the respiratory tract, and a characteristic feature is pain in the chest. Later a syndrome suggestive of tuberculosis is present.¹ In general, the symptoms will be the same as those seen in any other chronic generalized debilitating illness. The disease usually follows a steady downward course, with cough, chills, fever, anemia, leukocytosis, asthenia and loss of weight. Hemoptysis is common. Occasionally sinuses may appear in the thoracic wall, if the pleura becomes involved, but this is less common than in actinomycosis.¹⁶

16 Smith, D. T. Pulmonary Mycoses, Clinics 4:994, 1945

When the skin is secondarily involved, the lesions occur most frequently on unexposed parts, in contrast with the sites seen in the primary cutaneous disease. These lesions usually start as deep subcutaneous nodules, which soon break down, ulcerate and display the typical elevated violaceous margins. Occasionally milium abscesses of the skin and subcutaneous tissue may result in the formation of larger localized abscesses, which may contain 1 quart (about 946 cc) or more of pus⁸

Martin and Smith⁷ stated that in over 50 per cent of the proved and presumptive cases of systemic blastomycosis, the first symptoms were referable to the respiratory tract. In 4 per cent the primary lesion followed an injury of some kind, in 19 per cent a cutaneous lesion was noted first, and in 23 per cent the earliest symptom was a subcutaneous nodule or abscess. In the latter group, the sites of the original nodules were seen to be so variable that the evidence strongly supported the theory that the portal of entry was the lung and that the nodules resulted from dissemination of the fungi through the blood stream. These lesions may resemble either the tuberculous "cold" abscesses or the acute pyogenic type.

In a review of 63 cases in which there was evidence of bone involvement, of which group 6 of the patients recovered, Jones and Martin¹⁷ observed that in 13 of the patients the primary complaint was pain in the back or about the joints of the extremities. The foci of infection in the bones of the extremities, if located near the epiphyseal lines, may extend into joints and form pyarthroses, which in turn may be attended with drainage to the surface through chronic sinuses. Paravertebral or psoas abscesses may form from extension of lesions of the spine.

Usually the patient succumbs with a widespread infection involving not only his lungs, bones, skin and soft tissues, but also the lymph nodes, spleen, liver and kidneys. In some cases, the central nervous system, prostate gland, heart and peritoneum have been affected.

The physical signs in pulmonary blastomycosis may resemble tuberculosis, pulmonary abscess or neoplasm. Commonly, the signs are not as striking as the extent of the lesion might suggest.

PATHOLOGIC CHANGES

In the skin, decided and irregular thickening of the prickle cell layer is a feature. Also commonly noted are epidermal abscesses, in which the budding fungus cells may be seen associated with small round cells, red

¹⁷ Jones, R. R., Jr., and Martin, D. S. Blastomycosis of Bone. A Review of Sixty-Three Collected Cases, of Which Six Recovered, *Surgery* 10: 931, 1941.

blood cells, debris, neutrophils and giant cells. A cellular infiltrate and interstitial and parenchymatous edema of the underlying cutis are present.¹ The epithelial hypertrophy may be so apparent as to suggest carcinoma. In either cutaneous or generalized blastomycosis, the most characteristic reaction to the organism is abscess formation, although chronic inflammation, with giant cells, necrosis and fibrosis, may predominate.³

In the systemic disease, the lungs are more commonly involved than any other organ, most writers have stated that the incidence is more than 90 per cent. Friedman and Signorelli⁸ quoted Wade and Bel's analysis of 27 cases, in which they observed pulmonary lesions in 26, 96 per cent of the total. They stated that bones and joints are affected in 50 to 60 per cent of the studied cases, with most frequent involvement of the vertebrae, ribs and skull. The liver, spleen and kidneys are involved in 40 per cent of cases, the central nervous system in about 30 per cent and the prostate gland in 20 per cent, however, hepatic and splenic lesions are usually small and unimportant.³ Among other organs less frequently invaded are the tongue, larynx, epididymis, heart and pericardium. Unlike the involvement in actinomycosis and South American blastomycosis, the gastrointestinal tract is little affected in this disease. Interesting reports of a blastomycoma affecting the cerebellum¹⁸ and of another which was described as intravertebral and intrathoracic¹⁹ have been published. Another unusual case²⁰ was that of a woman in whom the disease developed in the pelvis after she had been suffering from pulmonary blastomycosis for two years. Surprisingly, this patient made a good recovery following panhysterectomy, despite the fact that originally she had a high titer of serum antibodies.

The evolution of the disease following pulmonary invasion is probably closely akin to tuberculosis. A primary complex may be established in the lungs or bronchial glands.¹¹ Jones and Martin¹⁷ stated that the pulmonary infection appears first in the bronchi and these lesions spread to become associated with bronchopneumonia in the adjacent pulmonary tissue. Enlargement of the mediastinal lymph nodes without obvious parenchymal involvement has been noted in a few cases of early disease.¹⁶ In most instances, dense parenchymatous masses are present in the lung.

18 Craig, W. M., and Carmichael, F. A. Blastomycoma of the Cerebellum. Report of a Case, *Proc. Staff Meet., Mayo Clin.* **13** 347, 1938.

19 Craig, W. M., Dockerty, M. B., and Harrington, S. W. Intravertebral and Intrathoracic Blastomycoma Simulating a Dumb-Bell Tumor, *South. Surgeon* **9** 759, 1940.

20 Hamblen, E. C., Baker, R. D., and Martin, D. S. Blastomycosis of the Female Reproductive Tract. Report of Case, abstracted, *J. A. M. A.* **105** 1551 (Nov. 9) 1935.

and may be located near the hilus, projecting into the lung fields in an irregular manner, often suggesting a neoplasm. Having entered the blood stream from the lung, or the skin, the organisms may be disseminated throughout the body to produce multiple metastatic foci, these, in their turn, may cause further infection of the blood stream and reinfection of the lungs and other tissues. When the infection is carried via the hematogenous route, the pulmonary shadows may resemble miliary tuberculosis. Cavitation sometimes occurs, but the cavities are usually small. Active pleurisy or pleural fibrosis is usually encountered.¹

In bone the infection may be localized or diffuse osteomyelitis, periostitis or arthritis. In the long bones the primary focus usually is seen at the epiphyseal lines, and at times the areas of destruction may simulate infarcts. Microscopic sections show many fungi invading the marrow compartments, with the usual cellular reaction, necrosis of the marrow cells and bone destruction. As the osseous partitions disappear, the separate foci may become confluent and form abscesses with separation of sequestrums. The joint usually is infected by extension from a focus in adjacent bone. The process is overwhelmingly destructive in nature.

The tissue reaction to the presence of the organism may be variable. Usually the infected areas show round cell infiltration, not infrequently associated with polymorphonuclear leukocytes and giant cells. However, blastomycetes may be seen in tissues showing no histologic change, or the only alteration noted may be small areas of necrosis. Extensive necrosis with abscess formation is common. The typical gross lesions of the disease are the cutaneous ulcers, the deep and superficial abscesses and the tubercle-like nodules in the viscera.¹⁷

The close mimicry of tuberculosis by this disease is shown not only in the history, clinical course and physical signs, but extends even to the microscopic appearance.¹¹ Miller²¹ expressed the belief that, except for the presence of blastomycetes, the lesions are essentially the same, but Gaspar²² emphasized that in the mycotic infection the lesions are essentially abscesses, miliary or gross, surrounded by polymorphonuclear leukocytes. He stated that the rampart of round cell infiltration seen around the site of a tubercle is entirely missing in the large majority of blastomycotic foci, and concluded that the inflammatory reaction to the blastomycetes might readily be called a suppurative granuloma. Giant cells of the Langhans type may be noted at the periphery of the lesion, and the nuclei commonly have a central position.¹ At times the giant

21 Miller, W. S. Reticulum of Lung. Its Similarity in Blastomycosis and Tuberculosis, *Am J Path* 3: 315, 1927.

22 Gaspar, I. Blastomycotic Meningo-Encephalitis, *Arch Neurol & Psychiat* 22: 475 (Sept.) 1929.

cells show the inclusion of blastomycetes, both active and dead, within their protoplasm, as many as 12 being counted in some ¹⁰

DIAGNOSIS

A definite diagnosis can be established only by identifying the causative organism. A multiplicity of lesions, especially when the lungs, bones and skin are involved, suggests a mycotic infection. Failure to demonstrate *B. dermatitidis* in the sputum or in direct smears of pus does not necessarily exclude the diagnosis, since the organisms at times may be difficult to observe.

Cultural studies are most important in identifying the particular organism. Excellent tables to differentiate the various fungi on histologic and cultural grounds have been published in the literature ²¹ In addition biopsy of cutaneous lesions will often clear up any confusion. Inoculation of animals is often an additional aid.

Friedman and Signorelli⁸ claimed that for an unequivocal diagnosis the organism must be identified in a direct smear from the available lesion, it must be grown on suitable culture mediums and biopsy must reveal the typical histologic changes and the causative agent. Baker²⁴ stated the belief that a biopsy which meets these requirements is sufficient for absolute diagnosis, while Lewis and Hopper¹ stated that if the budding micro-organism is observed in a direct preparation the diagnosis can be made with certainty. On the other hand, Smith²³ declared that the appearance of the organism in the tissue is often not sufficiently characteristic for identification.

Fortunately, further diagnostic procedures are available in the form of the intracutaneous sensitivity test and the complement fixation reaction, as advocated by Martin and his group. Agglutination tests have also been described, but have not proved as useful. Despite all these valuable means of investigation, however, the diagnosis is often made only by the histologist after an autopsy.

THE INTRACUTANEOUS TEST

Jones and Martin¹⁷ described the technic as follows:

The skin tests are done with a heat-killed vaccine, which is prepared by suspending in sterile saline solution the yeastlike organisms from a culture of *B. dermatitidis* grown on blood agar at 37 C. This suspension is centrifuged in a Hopkins tube and the sediment suspended in enough saline solution to make a

23 Smith, L. M. Blastomycosis and the Blastomycosis-Like Infections, *JAMA* 116 200 (Jan 18) 1941

24 Baker, R. D. Tissue Reactions in Human Blastomycosis. Analysis of Tissue from Twenty-Three Cases, *Am J Path* 18 479, 1942

1:1,000 dilution by volume. The standardized suspension is heated to 60 C for four hours and tested for sterility by heavily inoculating a blood agar slant and incubating at 37 C for at least ten days. Tricresol, 0.35 per cent, is added as a preservative. This material is used for skin testing by injecting 0.1 cc intracutaneously. Usually an area of erythema appears about the site of injection within fifteen to twenty minutes. This reaction is not specific and is found in patients having pulmonary disease of other types. The characteristic positive, beginning after twelve to twenty-four hours and reaching a maximum in two to four days, resembles closely a positive tuberculin reaction. In very allergic patients a sterile abscess may form at the site of inoculation. The occurrence of a positive reaction may be taken as presumptive evidence of the presence of blastomycotic infection, and this diagnosis is strengthened further by the finding of complement-fixing antibodies in the serum of the patient.

However, in the presence of blastomycosis the reaction is not always positive and there is anergy in cases of terminal disease.¹⁶

THE COMPLEMENT FIXATION REACTION

The test specific for *B. dermatitidis* can be done in any laboratory equipped to do Wassermann tests of the blood.¹⁷ The proportions of material and reagents are the same as those used in the Wassermann test except for the substitution of the fungus suspension for the beef heart antigen. Martin and Smith⁷ stated that the technic utilizes as antigen a saline suspension of blood agar cultures of the living yeastlike organisms. The dose of antigen used for each series of tests is calculated by determining the anticomplementary titer of the freshly prepared suspension. The antigen prepared in this way has the disadvantage of having a comparatively weak combining titer and necessitates using a freshly prepared antigen for each test. This does not make possible accurate comparisons of antibody content. A falsely positive reaction in patients who did not have blastomycosis was never obtained, however, the reaction is not positive in all cases of true infection.

ROENTGENOLOGIC OBSERVATION

Although they are not at all characteristic, roentgenograms of the chest may be suggestive of a mycotic rather than a tuberculous lesion—in the hilar distribution of the lesions, in the fact that the lesions are coarser and do not reach the periphery and in that they may show more calcification of hilar distribution than in tuberculosis.¹¹ However, the disease may present decided variation in the type of pulmonary infiltration.

Roentgenologic studies of bone lesions reveal a decided osteolytic reaction, commonly close to the epiphysial lines when long bones are involved, with or without abscess formation. Involvement of the neighboring joint may be revealed. When blastomycosis is suspected, roentgenograms of the entire skeleton should be made.¹⁶

DIFFERENTIAL DIAGNOSIS

The clinical picture of cutaneous and systemic blastomycosis is never so clear that it cannot be confused with many other diseases⁸

The cutaneous variety is most often mistaken for squamous and basal cell carcinomas, tuberculosis verrucosa cutis, nodular ulcerative

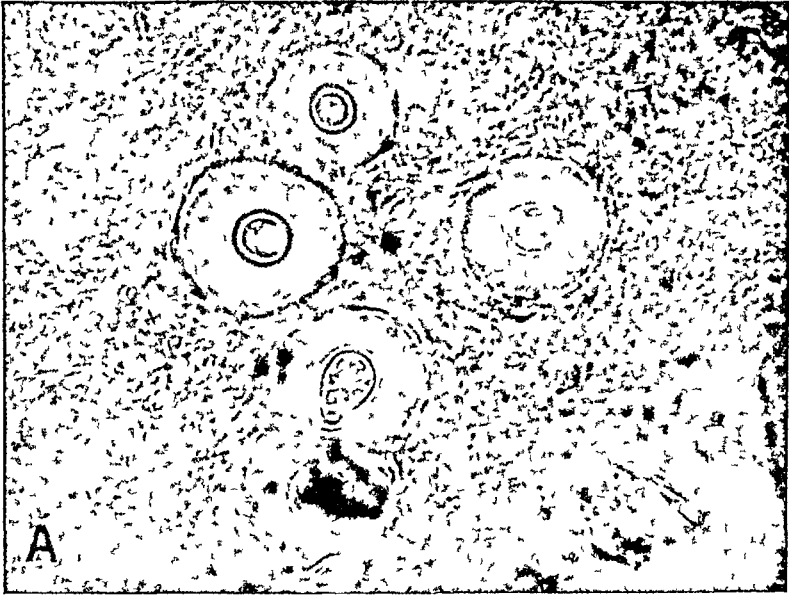


Fig 3—*Cryptococcus neoformans* A, pus containing the round thick-walled budding fungus surrounded by a capsule ($\times 850$) B, india ink preparation of spinal fluid, showing the budding fungus surrounded by a capsule ($\times 821$)

syphilids, anthrax, granuloma inguinale, bromoderma, iododerma, tinea barbae and other fungus infections

The systemic disease may simulate other mycoses, such as cryptococcosis, South American blastomycosis, sporotrichosis, actinomycosis,

moniliasis and coccidioidomycosis. In addition, pulmonary abscess, sarcoidosis, malignant neoplasms, pneumoconiosis, tularemia, lymphoblastomatous diseases, syphilis, pyemia, osteomyelitis and psoas abscess may have to be excluded. However, in the vast majority of cases

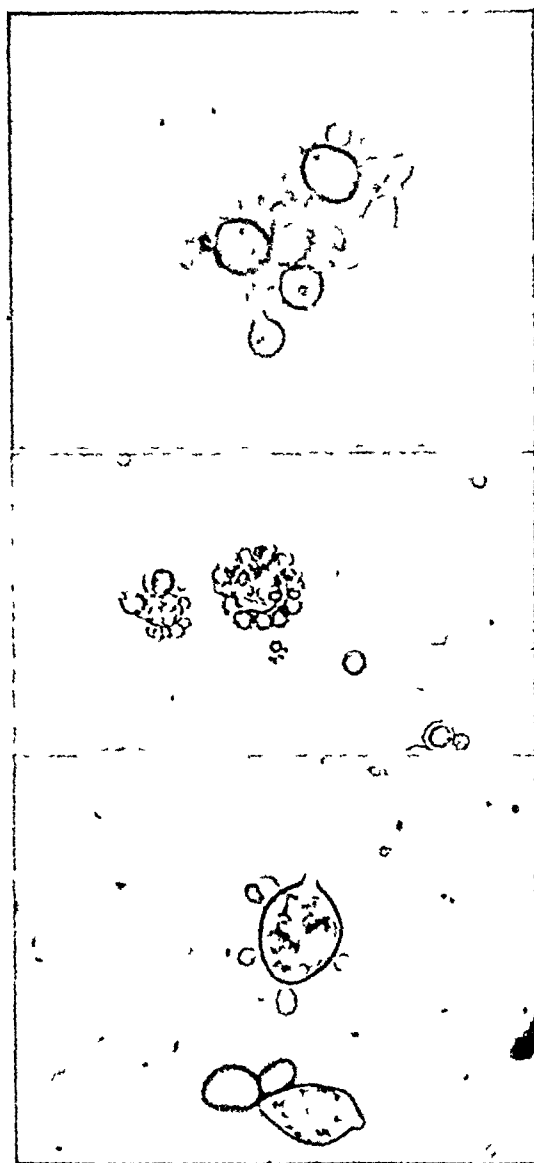


Fig 4—*Blastomyces brasiliensis*. Multiple budding forms from beef infusion glucose agar at 37 C ($\times 700$)

the disease with which it is likely to be confused is tuberculosis. The mycoses simulate tuberculosis more closely than does any other disease.

DIFFERENTIATION OF *B. DERMATITIDIS* FROM OTHER FUNGI³

As previously stated, *B. dermatitidis* is demonstrated in the tissues as thick-walled double-contoured round or oval cells, 8 to 20 microns in diameter, and its most salient characteristic is the fact that it multiplies

only by budding and forms no mycelia or ascospores in such an environment (fig 1) It produces only a single bud from a parent cell When cultured, the fungus develops as a yeastlike organism, the tissue form, at 37 C, but changes to a filamentous moldlike organism at room tempera-



Fig 5—*Candida albicans* (in sputum) A, fresh preparation ($\times 300$) B, gram-stained preparation ($\times 1350$)

ture (fig 2) Therefore, specific identification of B dermatitidis depends on its differentiation from the other fungi which reproduce by budding, which are in the main the organisms of cryptococcosis, South American blastomycosis and moniliasis In addition, budding forms may be seen in histoplasmosis and sporotrichosis

Cryptococcus neoformans, the causative agent of cryptococcosis, as seen in the tissues resembles *B. dermatitidis*, in that it is an ovoid to spherical single-budding thick-walled yeastlike organism, 5 to 20 microns in diameter. It is, however, surrounded by a wide refractile gelatinous capsule (fig 3). The most important point which identifies it is that cultures of this fungus remain yeastlike regardless of the temperature at which they are grown.



Fig 6—*Histoplasma capsulatum*, from blood agar culture ($\times 700$)

Blastomyces brasiliensis, the causative organism of South American blastomycosis, on the other hand, has the same morphologic and cultural features as *B. dermatitidis*, but differs microscopically in the yeastlike phase, as it produces multiple buds from the surface of the parent cell (fig 4).

Candida albicans, the pathogenic fungus of moniliasis, is seen as small oval budding yeastlike cells, 2 to 4 microns in diameter, with or without

accompanying mycelial elements Unlike *B dermatitidis*, these cells are thin walled (fig 5)

Histoplasma capsulatum, the cause of histoplasmosis, differs from all other fungi pathogenic to human beings in that it is primarily a parasite of the reticuloendothelial system and is rarely seen extracellularly in

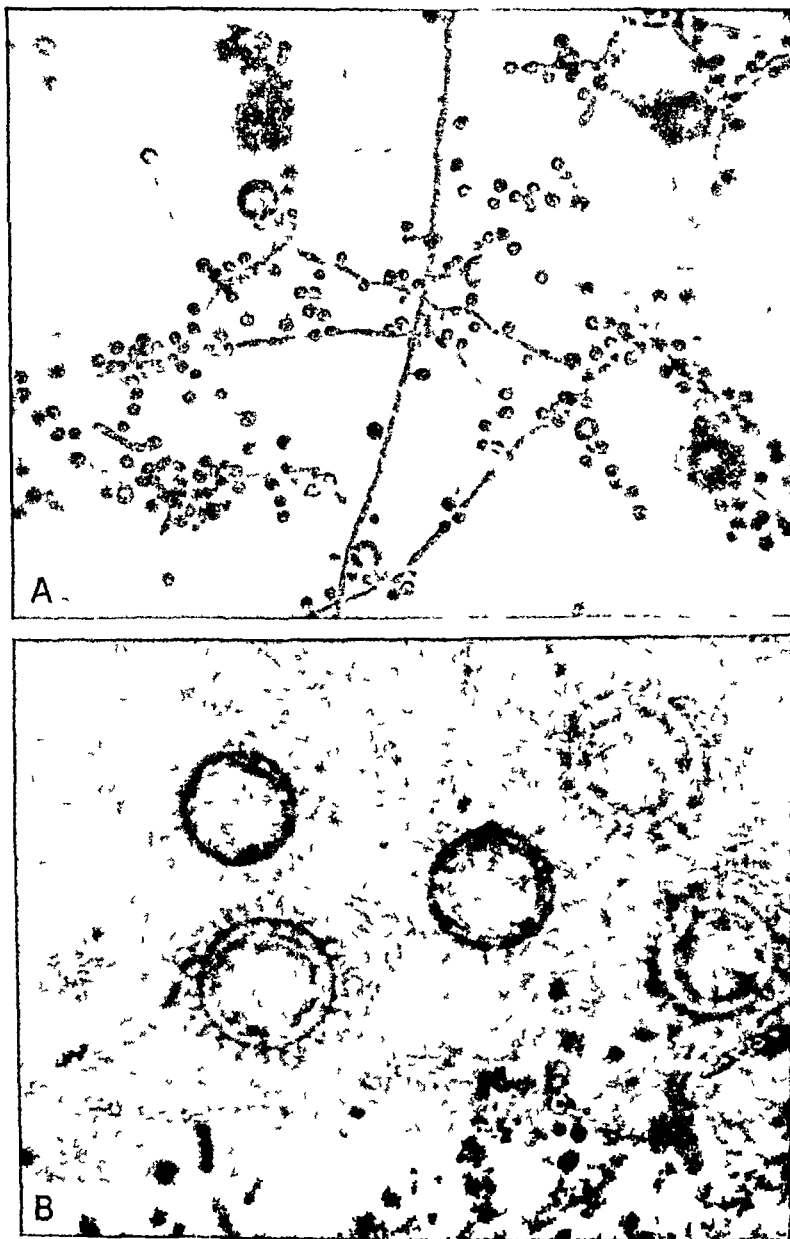


Fig 7—*Histoplasma capsulatum* (from Sabouraud's glucose agar) A, small smooth round to pyriform conidia ($\times 600$) B, large thick-walled round tuberculate chlamydospores ($\times 1500$)

tissue It is visualized as small oval bodies, 1 to 5 microns in diameter, in large mononuclear cells in the peripheral blood, sternal bone marrow, lymph nodes or tissues obtained by splenic puncture (fig 6) Budding forms are occasionally demonstrated On culture, characteristic large round tuberculate chlamydospores are observed (fig 7)

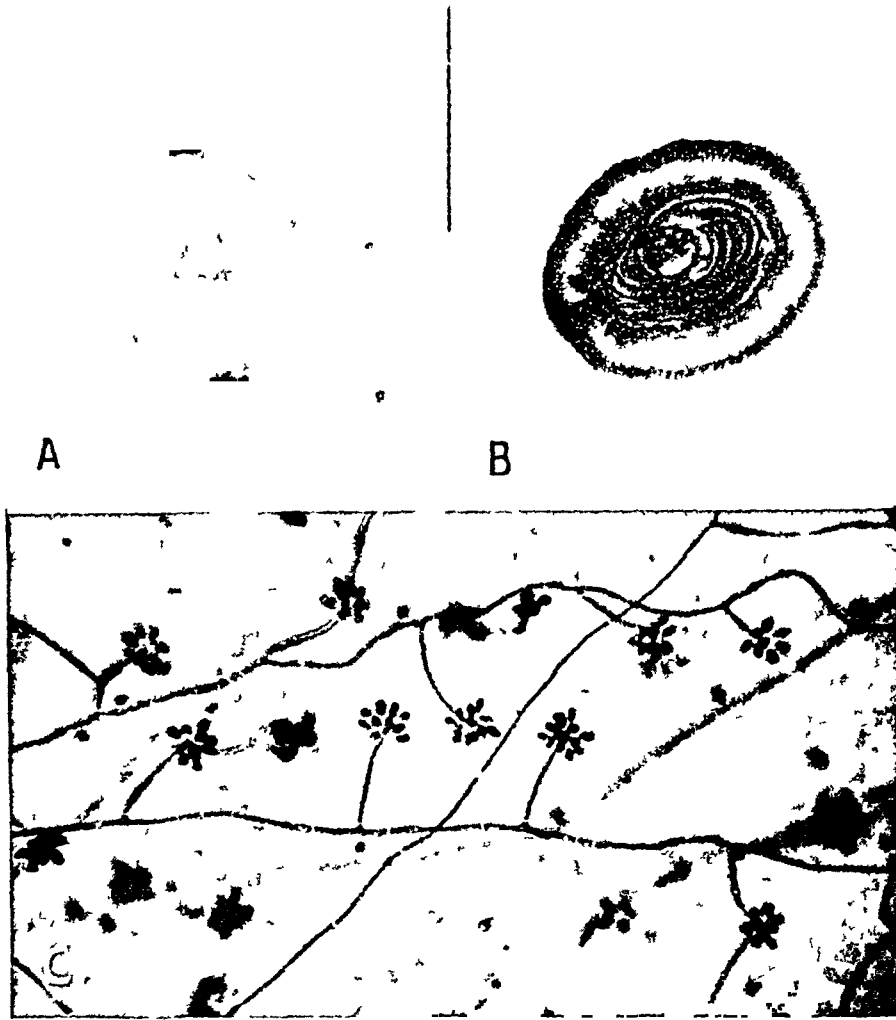


Fig 8—*Sporotrichum schenckii* A, white colony on Sabouraud's glucose agar, eleven days, at room temperature B, same stain on corn meal agar, eleven days, at room temperature with black pigmentation becoming evident C, delicate hyphae supporting conidiophores terminated with clusters of pyriform conidia Sabouraud's glucose agar slide culture (X 650)

Sporotrichum schenckii (fig 8), the organism of sporotrichosis, appears as small gram-positive cigar-shaped bodies within the polymorphonuclear leukocytes or giant cells, but usually they cannot be demonstrated in tissue After injection into mice, the tissue form develops in enormous numbers as small fusiform organisms, 3 to 5 microns in diameter, which reproduce by budding

Among the nonbudding mycoses are included actinomycosis, coccidioidomycosis, geotrichosis and chromoblastomycosis

It has commonly been considered that the fungi causing actinomycosis belong to two well defined biologic types, namely, anaerobic and aerobic. The anaerobic variety consists of a single species, *Actinomyces bovis*, a gram-positive and non-acid-fast organism. The aerobic type has been described as comprising several species of the genus *Nocardia* and is also gram-positive, with some acid-fast species. The diagnosis of



Fig 9—*Coccidioides immitis*. Round thick-walled endospore-filled spherule and collapsed spherule in pus ($\times 700$)

actinomycosis has been accepted on demonstration in biopsy of "sulfur granules" and separate mycelial segments, which reproduce by simple branching only. However, granules may occasionally be present in certain bacterial infections, usually by gram-positive *Staphylococcus aureus* or *Corynebacterium pyogenes* often associated with foreign bodies, and may simulate actinomycosis closely, accounting for the terms "botryomycosis" or "staphylococcic actinophytosis" for a nonmycotic disease.

Of interest in clarifying the present conception of actinomycosis is the recent article by Plummer²⁵ in which he emphasized that the two principal causative factors in actinomycosis as it appears in lower animals are the anaerobic or microaerophilic organism *A. bovis*, and the

25 Plummer, P. J. G. Actinomycosis. Histological Differentiation of Actinomycosis and Actinobacillosis, *Canad J Comp Med* 10:331, 1946



Fig 10—*Geotrichum* species Rectangular rounded end forms, arthrospores in sputum ($\times 375$)

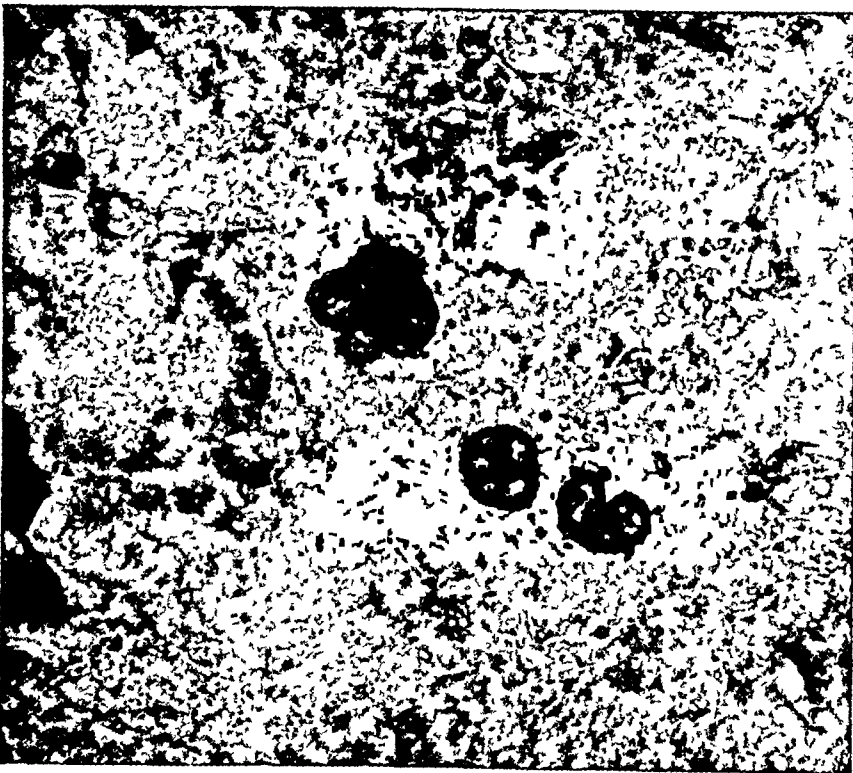


Fig 11—*Hormodendrum pedrosoi* (chromoblastomycosis) Dark brown septate bodies in pus from a lesion ($\times 825$)

aerobic bacillus, *Actinobacillus lignieresii*. He stated preference for the term "mycotic actinomycosis," or merely "actinomycosis," for the fungus disease and "actinobacillosis" for the bacterial type. He claimed that the importance of distinguishing between the two varieties of the disease is not always appreciated and stressed that in treatment this has resulted in disappointment and confusion. The iodine therapy so effective against actinobacillosis is of questionable value against mycotic actinomycosis. A *lignieresii* probably is the only known gram-positive organism associated with rosette formation.

Coccidioides immitis appears in infected material as a large nonbudding spherical thick-walled structure, 20 to 80 microns in diameter, which is filled with numerous small endospores (fig 9), at times, immature cells, containing no endospores, are all that can be seen by direct examination, and such forms may resemble the nonbudding cells of *B. dermatitidis*. Similarly, species of *Geotrichum* might be confused with Gilchrist's organism, if the less characteristic large spherical cells, 4 to 10 microns in diameter, predominate over the typical oblong or rectangular cells, 4 to 8 microns in size (fig 10). In chromoblastomycosis, the organisms appear as single or clustered round thick-walled dark brown bodies. These organisms multiply by splitting and not by budding (fig 11).

CLINICAL CONTRASTS BETWEEN GILCHRIST'S DISEASE AND OTHER MYCOSES³

In South American blastomycosis, the most characteristic single clinical feature in practically all cases is enlargement of lymph nodes. In the mucocutaneous type the primary lesion appears oftenest on the mucosal surface of the tongue, palate, gums, cheeks, lips or nose or on the skin around the mouth and nose, in the lymphangitic type localized enlargement of lymph nodes commonly occurs in the neck or supraclavicular or axillary regions. The visceral form is believed to effect its portal of entry through the intestinal tract and usually causes lesions in the liver, spleen, pancreas, adrenal glands, intestines and other abdominal organs, in sharp contrast with Gilchrist's disease. Involvement of the lungs develops in only 20 per cent of cases, and invasion of the skeleton is also far less frequent than in the North American disease. The infection, which is nearly always fatal, has not been reported from North America.

Cryptococcosis, while known as European blastomycosis, is not confined to Europe, and cases have occurred in the United States. It is thought that the fungus enters the body most frequently through the respiratory tract. A history of a mild infection of the respiratory tract

usually can be obtained from patients suffering from the commonest form of the disease, meningitis due to *Cryptococcus* Levin, in reviewing 47 cases from the literature, noted that the central nervous system was involved in 30 patients while pulmonary infection occurred in only 9. Bone lesions are rare. While primary pulmonary infection does take place, involvement of the mediastinum is rarely seen, another point of difference between this disease and North American blastomycosis. In cutaneous lesions the organisms are present in the absence of miliary abscesses, again in contrast with the observations in Gilchrist's disease. The local cutaneous type may heal, but other forms of cryptococcosis are commonly fatal.

C. albicans can be isolated so frequently from the throat, vagina, skin and intestines of healthy persons that a diagnosis of moniliasis often is difficult to substantiate. Pulmonary infection is indicated only if the fungi can be seen constantly on repeated examinations and other causative agents can be excluded. The organism causes thrush, perlèche, vulvovaginitis and a cutaneous infection which often involves the nails. Bronchial moniliasis is common, but usually benign, pulmonary moniliasis is rarer, but a more serious disease. Bone and joint invasion is unusual. Patients with the bronchial and pulmonary forms usually recover, although pulmonary moniliasis occasionally is fatal. The prognosis is hopeless in patients with endocarditis or meningitis.

Histoplasmosis rarely has been diagnosed before autopsy, and it has been considered to be uniformly fatal. In recent years there has been reason to believe that healing by fibrosis may occur, suggesting the possibility that patients with limited clinically unrecognizable lesions may recover. It has also been suggested that healed infection may be the cause of widespread minute calcified foci throughout the lung fields. The disease is often characterized by chronicity, fever, emaciation, anemia, leukopenia, splenomegaly, hepatomegaly, lymphadenopathy and ulcerations in the nasopharyngeal cavities and intestines. The bone marrow commonly is extensively involved. The lungs practically always are infected in cases of generalized disease, but the lesions usually are microscopic in size, the hilar lymph nodes may be enlarged. Histoplasmosis manifests itself most typically as a generalized disease, with involvement of the reticuloendothelial system.

Sporotrichosis usually presents such a typical picture that the diagnosis can be established by the clinical observations alone. It is characterized by the development in the lymph nodes, skin or subcutaneous tissues of nodular lesions which soften and break down to form indolent ulcers. The localized lymphatic form is the commonest, often being confined to one extremity. The disseminated form is rare, the first symptom noted is the presence of numerous hard subcutaneous nodules.

scattered on the body, suggesting infection of the blood stream. It is unusual for the latter lesions to ulcerate. Primary infections of the lungs and other viscera are extremely difficult to prove, and they occur, if at all, as rarities. Skeletal and visceral invasion, likewise, is rare. Of all the fungus diseases of human beings, sporotrichosis responds best to iodide therapy.

Actinomycosis is the commonest and geographically the most widespread of the systemic mycoses. It is commonly classified into cervicofacial, thoracic and abdominal forms. In the first type, which is the commonest, the organism usually gains its entry into the lower jaw, particularly in the region of an infected tooth or in the socket left by a recent extraction. It gives rise to the familiar "lumpy jaw," and abscesses and multiple sinuses finally develop. Infection of the lung commonly results in numerous draining sinuses in the thoracic wall, a rare observation in Gilchrist's disease, the ribs are invaded frequently. In the abdominal type, the first symptoms may suggest acute or subacute appendicitis. An indistinct irregular mass may be palpated, and sinuses may appear in the abdominal wall. Invasion of the liver may produce jaundice and give rise to hepatic abscesses. The infection may spread to the vertebral bodies, leading to compression of the spinal cord or the formation of a psoas abscess. The prognosis is best in the localized dermal and cervicofacial types, but it is grave in all other forms.

Coccidioidomycosis is probably the most infectious of the systemic mycoses, the majority of persons who live in endemic areas for any length of time acquire the infection. The greatest endemic focus of the disease is the San Joaquin Valley in California. Infection may result in primary coccidioidomycosis, which usually is an acute, but benign, self-limited disease of the respiratory tract, or in progressive coccidioidomycosis, which is a chronic, malignant and disseminating affliction. In the primary type the initial symptoms of a mild infection of the respiratory tract subside in one or two weeks, but in about 3 per cent of cases, allergic manifestations appear three days to three weeks after the termination of the febrile period. Fever reappears, and lesions resembling erythema nodosum or erythema multiforme occur. At times the primary infection may start on the skin or in the subcutaneous tissues. The disease in about 0.2 per cent of the cases of primary infection develops into the progressive, and usually fatal, form. When this happens, evidence of dissemination is observed some weeks or months after the onset of the primary infection. The lungs become invaded, followed later by involvement of the bones, joints, skin, subcutaneous tissues, internal organs, brain or meninges. The lesions are almost identical with those seen in Gilchrist's disease.

Geotrichosis has been described in only a few instances, but the fungus, like that of moniliasis, is not infrequently cultured from the mouths and intestinal tracts of normal persons. In the mouth, the disease resembles thrush. Bronchial geotrichosis is the most frequently recognized manifestation of the infection, and it behaves as a chronic benign type of bronchitis, with persistent cough and expectoration of a peculiar mucoid or gelatinous type of sputum. The rare pulmonary type simulates tuberculosis. The prognosis is usually good.

Chromoblastomycosis is a disease essentially confined to the cutaneous and subcutaneous tissues. It is characterized by the formation of warty nodules on the skin and later by prominent papillomatous vegetations, which may or may not ulcerate. The lesions usually are confined to the feet, legs and head. It is not a fatal disease.

PROGNOSIS

In cutaneous Gilchrist's disease the outlook is good as far as life expectancy is concerned, but rather unfavorable regarding the possibility of cure. Although many cures have been reported, recurrences are frequent, the results generally inconstant and the course of the infection chronic. Cases have been followed for as long as twenty years.⁸ The possibility of dissemination is ever present, but this, fortunately, occurs in a comparatively small percentage of cases. Occasionally a solitary blastomycotic lesion may be cured by surgical excision.

In systemic blastomycosis, however, all authorities agree that the prognosis is uniformly poor. Most writers have stated that the mortality rate is over 90 per cent within three to five years after onset. Fishman⁹ estimated the fatality rate as 83 per cent, but Martin and Smith⁷ stated that the percentage of deaths in published reports of cases is 92, if those cases which had been followed for less than two years are excluded. There are several cases on record in which real cures have been reported, but the results in the majority of these instances must be accepted with reservation, since the details are inadequate or the period of observation too short, it is entirely possible that at least some of the reported cures are the result of the immunologic response of the host rather than of the treatment employed.⁸

Experience with the complement fixation reaction indicates that the antibody titer is of importance in determining the degree of infection, a high titer indicates extensive infection, while a low titer or negative reaction in a patient with blastomycosis usually signifies that the infection is not widespread.⁷ A high antibody titer and a negative reaction to a cutaneous test indicate an unfavorable prognosis, a more favorable course can be anticipated when the reaction to the cutaneous test is positive and the reaction to the complement fixation test is negative,⁸ as is usually the case in the localized cutaneous disease.

TREATMENT

In general, the results of treatment of cutaneous and systemic blastomycosis are unsatisfactory and leave much to be desired⁸

In the cutaneous type, the lesions often respond temporarily to a multitude of therapeutic agents, but recurrences are frequent after cessation of active treatment. Iodides, orally and intravenously, have been extensively employed, usually with decided improvement in the majority of cases⁷

Potassium iodide, in saturated solution, is measured by drops and is administered orally in 30 cc of water. In the slow method, 3 drops are given three times daily after meals and the dose is increased by 1 drop per day (not 1 drop per dose), until the patient is receiving 20 drops three times daily. The dose is then reduced to the starting point and gradually increased again to the maximum dose of 20 drops. By the rapid method, the initial dose is 5 drops, given three times daily, and the dose is increased by 1 drop for each dose, or 3 drops each day. Treatment with the drug may be stopped when a dose of 20 drops is reached, or it may be increased to as much as 100 drops given three times daily. If symptoms of iodism appear, treatment with the drug should be discontinued until the symptoms have disappeared, treatment is then resumed, beginning with 5 drops per dose. Courses of treatment, by either the slow or the rapid method, may have to be continued for months and in some cases for years³. When the lesions do not respond to this type of treatment, Ormsby is quoted as having suggested the intravenous use of arsphenamine to render the organism more susceptible to the action of the iodides⁸

In cutaneous blastomycosis, the lesions are usually secondarily infected with bacteria and local applications of compresses and sulfonamide drugs are of value in controlling the bacterial contaminants. Roentgen therapy has been favorably advocated as an adjunct to iodide therapy³

Among a multitude of other measures which have been tried may be mentioned copper sulfate, silver nitrate, solid carbon dioxide, methylrosaniline chloride, lead iodide ointment, tincture of iodine, bichloride of mercury, phenol, radium implantation, curettement and cauterization.

Results of treatment of systemic blastomycosis have been even more unsatisfactory. Potassium iodide has been used more extensively than any other drug, but the results are discouraging⁷. It has usually had no effect on the progress of the disease, although temporary improvement and even a few cures have been ascribed to it. In some cases there has been incontrovertible evidence that actual harm accrued from its use, spread of the disease ensuing. If the patient's allergic reaction outweighs

the immunologic response to the infection, iodides are contraindicated. If the cutaneous test reveals hypersensitivity, a gradual course of desensitization should be undertaken, and only after that may small amounts of iodides be given with safety. From all present indications, best results are obtained when administration of iodides is supplemented by the judicious use of roentgen rays, suitable surgical procedures and desensitization with vaccines. Ethyl iodide inhalations have been employed with some success in a few cases.³

The proper dilution of vaccine for the first desensitization injection can be estimated from the size of the reaction observed in the cutaneous test. If the erythematous area is less than 1 cm in diameter, it is safe to administer iodides without desensitization. If the zone is about 2 cm in diameter, the vaccine should be diluted 1 to 100 for the first course, whereas, if the cutaneous reaction measures as much as 3 cm, the dilution recommended is 1 to 1,000 (which amounts to a 1 to 1,000,000 dilution of the original material). If the reaction is larger than 3 cm, it is unsafe to inject the vaccine unless it is diluted at least 1 to 10,000. The initial dose of the correct dilution should be 0.1 cc, and gradually increasing doses should be given no more than every other day. Treatment with iodides may be commenced cautiously after about two weeks of vaccine therapy, if the cutaneous test reveals a reduction in the degree of allergy. Vaccine injections should be continued during the first few months of iodide therapy.

Comparative serologic studies of different strains of *B. dermatitidis* indicate that they are antigenically homogenous, and a stock strain maintained on blood agar can be used as a source of skin-testing material, complement-fixing antigen and therapeutic vaccine.⁷

Martin and Jones²⁶ reported a cure in a patient who was treated with iodides, antiblastomyces rabbit serum, roentgen rays and introduction of maggots into an osteomyelitic sinus. Fishman⁹ in 1944 published a description of a case in which he attributed recovery to the use of ether, topically and rectally. However, Friedman and Signorelli⁸ observed this treatment to be of no value in their case. Cures following surgical excision of the most extensive focus of the infection have also been reported.²⁷

Antimony potassium tartrate, colloidal copper, methylrosaniline chloride, sulfonamide drugs and various other drugs have been utilized

26 Martin, D. S., and Jones, R. R., Jr. Systemic Blastomycosis. Report of a Case with Unusual Immunologic Findings, Well Two Years After Onset, Surgery 10: 939, 1941.

27 Hamblen, Baker and Martin.²⁰ Gillies, M. A Case of Blastomycosis, Canad. M. A. J. 26: 662, 1932.

by different observers Preliminary reports on the use of penicillin likewise have been discouraging

Supportive measures, such as rest, sunshine, vitamins and a nutritious diet, should always be provided, as spontaneous recoveries occasionally do occur ¹¹

All of the illustrations have been reproduced from the manual by Conant and his co-workers (Conant, N F , Martin, D S , Smith, ~~ED~~ T , Baker, R D , and Callaway, J L Manual of Clinical Mycology, Philadelphia and London, W B Saunders Company, 1944)

263 Somerset Street West

NORTH AMERICAN BLASTOMYCOSIS (GILCHRIST'S DISEASE)

II An Analysis of Canadian Reports and Description of a New Case of the Systemic Type

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IN THE preceding article was presented a study of North American blastomycosis based on a review of the literature. The purpose of this communication is to describe the results of a critical analysis of all previously reported Canadian cases and to add another report of a case to the literature.

Primrose¹ presented the first Canadian publication relating to the disease in 1909 though he had published an earlier report of this case in 1906 in the *Edinburgh Medical Journal*³. His paper dealt mainly with a further description of the same patient from Toronto, but also included notes on 3 additional cases. This patient, a 28 year old man of English birth, had a history of the disease dating back to January 1901. He had lived in Chicago for three years prior to the development of his disease, which involved the skin of the face, shoulders, neck and lower extremities—fourteen different cutaneous lesions in all. Iodide therapy caused a disappearance of the malady for over three months, and for the next four years his only manifestation of the infection was a lesion on the neck. This was excised in 1905, and he was free from further trouble for one year, when, after an injury to the right testis, a small abscess developed on each side of the scrotum. After rupturing spontaneously, typical blastomycotic patches developed, but soon these lesions disappeared, only to recur after another eighteen months. At this

1 Primrose, A. Second Report of a Case of Blastomycosis of the Skin, with Notes on Three Additional Cases of Blastomycetic Infection, Surg, Gynec & Obst 9 5, 1909

2 This footnote has been deleted

3 Primrose, A. Blastomycosis of the Skin in Man, Edinburgh M J 20 215, 1906

time the patch on the right side was attached to an indurated nodule which involved the epididymis. In November 1908 the cutaneous scrotal lesions, together with the right testis and epididymis, were excised. There was no recurrence at the time of the final examination six months later. Scrapings from the cutaneous patches were said to reveal highly refractile double-contoured bodies, which showed evidence of multiplication by budding. It was stated that blastomycetes were demonstrated also in the excised tissues. Inoculation of guinea pigs was unsuccessful. The organisms were restricted practically to the milary abscesses, and the histologic description was in keeping with that of Gilchrist's disease. However, Primrose made the statement that blastomycetes in cultures show no mycelium. Apparently he did not realize that at room temperature the fungus is transformed into its moldlike mycelial phase. While he presented an excellent discussion of the differences between the fungi of coccidioidomycosis and the "Chicago disease," as North American blastomycosis was also termed, he was not acquainted with the definite differentiation between the organism of cryptococcosis (European blastomycosis) and that of Gilchrist's infection. Despite this serious inadequacy in the cultural studies, it would seem that this report of a case merits inclusion in the category of presumptive cases of cutaneous Gilchrist's disease.

The second case briefly described by Primrose was that of a market gardener, 38 years of age, in whom cutaneous lesions developed on the right wrist and the front of the neck. He had been looking after a young heifer with a rather extensive cutaneous disease. The author stated that he saw typical blastomycetes in scrapings, and the lesions disappeared with iodide therapy. However, no proof of the diagnosis was presented, so that there was inadequate information given to allow acceptance of this case as one of North American blastomycosis.

Primrose's third case was that of a farmer of 44 years, in whom decided swelling and limitation of movement of the right elbow developed shortly after trauma to the part in October 1907. A biopsy was performed, and it was stated that blastomycetes, exhibiting the characteristic features of the budding form, were demonstrated and successful cultures were made. The affected tissue was later curetted, but no direct connection with the elbow joint was determined. In May 1908 the elbow presented an appearance like that of a tuberculous joint with fusiform enlargement, though the wound had healed. Treatment with potassium iodide had produced no benefit. Amputation was performed, and no recurrence had resulted at the time of the publication. While the disease in this case may have been diagnosed correctly, the details are insufficient for acceptance, especially as the history was not too characteristic.

A fourth case, in which autopsy was performed, was mentioned briefly by Primrose, who did not present more than a cursory summary of it as he understood that it was to be published in detail by Prof J J MacKenzie. Unfortunately, this expectation was not realized. It concerned a male patient whose disease was diagnosed as generalized blastomycosis, who presented abscesses in the neck, spleen and kidney, bronchopneumonia and involvement of the meninges. No proof of the diagnosis was advanced.

In 1911 Shepherd and Rhea⁴ published an outstanding article, in which they reported a case of the systemic disease. Their patient was an Italian man, aged 25 years, who presented himself at their Montreal clinic on Aug 2, 1910, with an eruption on the nose and on the right side of the face, a discharging sinus leading down to diseased bone at the sternal end of the right clavicle and a fluctuating swelling over the second lumbar vertebra. The onset dated back four months. The authors suspected blastomycosis from the appearance of the cutaneous lesions and a biopsy was said to have revealed blastomycetes. There was no response to treatment with iodides. One month later examination uncovered evidence of a lesion in the base of the right lung, but the sputum did not reveal the organism. Pus evacuated from the abscess in the lumbar region, however, did disclose the fungus on culture. Before the patient's death, on Dec 27, 1910, about nine months from the onset of the illness, many other lesions developed.

Autopsy revealed involvement of the skin, bones, pleurae, lungs, peritoneum, lymph nodes, kidneys, left adrenal gland, prostate gland and esophagus. The osseous invasion included the left tibia, the right clavicle, femur, humerus and ulna and the bones of the right foot. Microscopically the lesions were characterized by necrosis of the tissues, cellular infiltration, giant cells and many spheres with encapsulating membranes. The organisms were numerous, were seen both extracellularly and within the cytoplasm of the giant cells and showed various stages of budding. No mycelia or endospores were seen. The organism was recovered in cultures several times, and lesions were produced in mice. The authors stated that the microscopic examination of cultures revealed branching mycelia. No mention was made of demonstrating the yeastlike form on blood agar at 37 C.

At the conclusion of this paper Ormsby and Gilchrist discussed the case and apparently accepted the diagnosis. The diagnosis would seem to have been established in this report, though the details of the cultural studies were not completely adequate. Shepherd, in his final discussion,

⁴ Shepherd, F J, and Rhea, L G. A Fatal Case of Blastomycosis, *J Cutan Dis* 29 588, 1911.

stated that he had had another case six months previously, in which the disease was not recognized until autopsy. This case was not reported, and no details were given.

In 1915 McKenty and Morgan⁵ presented a paper in which they described 4 of the 6 cases found in the records of the Royal Victoria Hospital in which the disease was diagnosed as Gilchrist's disease. However, in none of these cases was adequate proof submitted to permit acceptance of the diagnosis as proved or presumptive. The first case concerned an Italian laborer, aged 48 years, in whom a hard swelling, about the size of a hazelnut, developed just posterior to the anus one year before he was seen by the authors. This lesion was curetted, enlarged glands appeared in the inguinal region, and a sinus developed. It was stated that pus from the inguinal area showed typical double-contoured organisms, but no mention of budding was made and no cultural studies were performed. Sections revealed decided epithelial hyperplasia, polymorphonuclear leukocytes and giant cells, and the organism was seen in scattered areas. The patient was reported to be improving. In the second patient, a farmer of 63 years, an ulcerating cutaneous lesion developed on the malar eminence on one side of the face shortly after he had suffered a slight laceration from a branch of a tree. The lesion was excised, and a cure resulted. The pathologic report revealed decided hyperplasia of the epithelium, small abscesses and giant cells. The only statement bearing on a specific diagnosis was the bald declaration that typical blastomycetes were seen.

McKenty and Morgan's third case was that of an Italian laborer, aged 43 years, in whom a small lesion developed close to the external canthus of the right eye in September 1909. This lesion soon ulcerated, and in a few months a diffuse swelling appeared in the right temporal area, which was incised. It was stated that a peculiar condition was observed in the underlying bone. Headaches and chills developed, and the patient died on June 14, 1910, less than three months after admission to the hospital. Pus from the original lesion was said to have disclosed many typical blastomycetes. The autopsy was reported as demonstrating mycosis of widespread type, involving the skin, frontal and temporal bones, ethmoidal and sphenoidal sinuses, basal meninges, lungs, pleurae, pericardium, spleen and retropharyngeal tissues. The organism was a spherical body, with a well defined capsule and chromatic granules in its interior. It multiplied by fission, one cell producing two others or more, a culture showed a growth which was definitely mycelial. While multiple budding is characteristic of South American blastomycosis, this disease has never been reported from North America. This description

⁵ McKenty, F. E., and Morgan, D. Blastomycosis, *Ann Surg* 61:513, 1915.

would definitely exclude acceptance of the organism as Gilchrist's fungus

Their fourth case was that of a 32 year old wife of a farmer, in whom a small lesion developed on the tip of the nose two months prior to examination by the authors. This gradually enlarged, similar lesions appeared over other areas of the nose, and coalescence occurred, until the lower half of the organ was involved. The edges faded gradually into the surrounding skin in places, but in other areas the edge was heaped up and was dark brown. While this description suggests cutaneous Gilchrist's infection, unfortunately, the writers presented no proof of diagnosis other than the statement that examination of the pus revealed the organism.

No further articles on the subject emanated from Canada until 1930, when McKee⁶ published his paper on blastomycosis of the eye. This had been read before the Thirteenth International Congress of Ophthalmology at Amsterdam, Netherlands, in September 1929. In this presentation the frequency of involvement of the eyelids in blastomycotic dermatitis with the production of ectropion was discussed. This was exemplified in Shepherd and Rhea's⁴ case. While McKee stated that his group had seen "a number of cases, evidently blastomycosis in which the organisms were demonstrated only after many examinations, or not at all," his paper did not include a report of a case.

In 1932 Crich⁷ of the Lockwood Clinic presented a report of an unusual case of the disease, involving the gingiva and the jaw. He stated that in only 1 other case reported had the infection begun in the gums, and in that instance the patient had been in the habit of carrying a splinter of some sort in his mouth, suggesting the possibility that the infection had been introduced in that manner. His patient had been given to plucking blades of grass or hay and keeping them in his mouth. The case was that of a 56 year old storekeeper, who presented himself on Nov. 25, 1931, with decided epithelial hyperplasia around the socket of the lower left central incisor, which had been extracted because of a surrounding gingival infection just prior to examination. A small ulcer was noted on the buccal surface, and a sinus within this ulcer communicated with the socket. The submaxillary glands were swollen and hard and appeared to be adherent to the lingual border of the mandible. He had suffered toothache on several occasions prior to extraction of the tooth. More than one month before his examination, the patient had been confined to his home for two weeks with fever, cough and night sweats. Hemoptysis had occurred once. Roentgeno-

⁶ McKee, H. Blastomycosis of the Eye, *Canad. M. A. J.* **22**: 501, 1930.

⁷ Crich, A. Blastomycosis of the Gingiva and Jaw, *Canad. M. A. J.* **26**: 662, 1932.

graphic examination of the chest revealed extensive infiltration of the apex of the left lung, resembling tuberculosis. Roentgenograms of the teeth disclosed entire loss of bone in the area from which the tooth had been removed. On December 1, a biopsy of the gingival tissues was performed, and the report from the laboratory of the Department of Health of Ontario included a diagnosis of blastomycosis, budding having been demonstrated. A few days later lesions appeared on the legs, resembling erythema nodosum.

The case was then referred to Dr. Gordon New at the Mayo Clinic, and the diagnosis was said to have been confirmed on biopsy by Broders. New employed surgical diathermy to eradicate the lesion in the jaw and subsequently used irradiation, with roentgen rays and radium. The nature of the pulmonary lesion was a matter of uncertainty, as the sputum did not present tubercle bacilli on two occasions and fungi were not demonstrated. Crich postulated that if the pulmonary infection was tuberculous the gingival lesion represented a primary focus of blastomycotic infection, whereas, if pulmonary blastomycosis was the cause the lesion in the mouth was secondary and probably due to the fungi being present in the mouth from sputum rather than to hematogenous spread. In a personal communication, Crich⁸ stated that the patient recovered completely and was still alive. The nature of the pulmonary lesion was never definitely determined.

There was no comment in the paper about the details of the biopsy done at the Mayo Clinic and no statement about the investigation of the sputum at the clinic. Likewise, no cultural studies were described. The reaction to tuberculin was also not stated. Despite these shortcomings, the diagnosis would appear to be acceptable as presumptive, especially as it was confirmed by New and Broders. The nature of the pulmonary involvement remains in doubt.

In 1933 Gaumond⁹ reported a case from Quebec City, Canada, but this report was confusing and the diagnosis unacceptable. It concerned an 11 year old boy admitted to the hospital in June 1931 with the complaints of weakness, cough, severe pain in the left costovertebral region and swelling the size of an orange in the right temporal region, which was violaceous and was suppurating from several points. This abscess was incised and curetted and healed completely. *Staphylococcus aureus* was seen in the pus. While tests of sputum gave negative results, the diagnosis was considered to be tuberculosis, especially as a roentgenogram revealed a supradiaphragmatic shadow in the left lung. In a short time a soft red tumor developed in the posterior region of the left

⁸ Crich, A. Personal communication to the authors.

⁹ Gaumond, E. Blastomycose generalisee mortelle, *Bull. Soc. med. d'hop. Univ. de Quebec*, 1933, p. 322.

hemithorax, and subsequently several other similar tumors appeared close by. These opened spontaneously early in 1932, discharging thick yellow pus. Pallor, weakness, anorexia, fever, cough, expectoration and dyspnea featured the clinical course of the case. While a lesion developed in the base of the right lung, for a time the patient improved and the tumors disappeared. Peculiarly, the patient died suddenly on May 14. Mycosis of some type had been considered the likely diagnosis, and the patient was treated with iodides and ultraviolet and roentgen rays. Inoculation of a guinea pig did not reveal tuberculosis. A biopsy of one of the tumors showed that it was a polymorphous granuloma, with small abscesses scattered in the skin. It was thought probable that the lesions were due to a type of mycosis, caused by one of the group of *Blastomyces* organisms. Cultures of the pus and sputum showed typical yeast cells, with no true filaments. No granules were ever seen.

Postmortem observations included pleural adhesions, foci of bronchopneumonia, a large amount of fluid in the abdomen, thick gelatinous pus between the liver and the diaphragm, a few small abscesses in the liver and an abscess in the spleen. Histologic examination was said to show that the hepatic lesion was a mycetoma, presenting the characteristics of actinomycosis, and that the foci in the lungs and spleen were of the same type. Cultures from the pus in the subdiaphragmatic region revealed yeast cells and mycelial filaments, but it was not possible to identify these organisms positively. It was stated that the postmortem diagnosis was mycetoma, with lesions in the liver, lungs, spleen and skin, presenting the macroscopic and microscopic features of actinomycosis, although no granules could be seen and cultures showed yeast forms closely resembling blastomycetes. From the report it is difficult to understand why actinomycosis was considered so seriously, considering the presence of yeast cells and the absence of granules.

In the same year, 1933, Gillies¹⁰ reported a case from the Manitoba Sanatorium. His patient was a 15 year old boy, whose first complaint was noted in February 1926, when the left foot became swollen and painful. Within three weeks the lesion broke down, discharging dark green pus, and on May 19 the foot was incised and the fourth and fifth metatarsal bones were removed. The process was thought to be tuberculous. A fortnight later sores appeared on the back of the right leg and on the right arm. On admission to the hospital on July 21, the complaints included cough, expectoration of blood-streaked purulent sputum, pain in the chest and back, sore throat, hoarseness, epigastric distress and loss of 30 pounds (about 13.6 Kg.) in weight. The boy was ob-

10 Gillies, M. A Case of Blastomycosis, *Canad. M. A. J.* 29: 183, 1933.

served to have large granulating ulcers on the right leg, right arm and left foot, which was the site of an extensive osteomyelitis. Roentgenograms revealed widespread disease throughout both lungs, but tubercle bacilli were not seen in the sputum. Following amputation of the left foot on August 9, the pathologist made a diagnosis of tuberculous infection of the bones and soft tissues. A definite improvement in the patient's general health then occurred, but the ulcers on the right arm and leg failed to heal.

Gillies stated that in November a diagnosis of blastomycosis was made by Dr. D. F. MacRae and was confirmed by observation of the fungus in smears and cultures from the ulcers. A series of intradermal tuberculin tests then elicited negative reactions. Administration of iodides and heliotherapy resulted in the healing of the ulcers within one month. Roentgenograms of Jan. 3, 1927, were described as revealing the lungs to be clear and fairly normal in appearance. Before blastomycosis was suggested as a diagnosis all expectoration had ceased. The patient was discharged on February 24, in good health, and had remained well for the six years prior to the publication of the report. The author concluded that the early amputation of the foot, the worst focus of the disease, apparently enabled the natural defenses of the body to overcome the remaining infection. Unfortunately, the absence of any morphologic description of the organism and of any details of the cultural studies detracts from this otherwise excellent presentation. While the history in the case suggests the strong possibility that this was an example of systemic Gilchrist's disease, with recovery following surgical treatment, the diagnosis was not proved, but it might be accepted as presumptive.

In 1936 Beregoff-Gillow¹¹ published a paper in which she reported the observation of fungi in the sputum of 2 patients in the medical service of the Women's General Hospital, Montreal. The histories were not presented, but the claim was made that blastomycosis was established as the diagnosis in each instance on the basis of laboratory observations. In the first case she stated that budding double-contoured organisms of the order *Saccharomyces* were demonstrated. It was reported that the organism fermented all sugars, a statement contrary to the characteristics attributed to Gilchrist's organism¹². In addition, guinea pigs and rats were successfully inoculated intravenously. The

11 Beregoff-Gillow, P. The Importance of Early Diagnosis in Mycotic Diseases, with Special Reference to Blastomycosis, with a Brief Report of Two Cases, *Canad. M. A. J.* 34: 152, 1936.

12 Friedman, L. L., and Signorelli, J. J. Blastomycosis. A Brief Review of the Literature and a Report of a Case Involving the Meninges, *Ann. Int. Med.* 24: 385, 1946.

growth of this organism on glucose agar was stated to be luxuriant, smooth and white, consisting of round and oval cells and some budding, without any mycelium. The complete failure to describe the mycelial moldlike phase when grown at room temperature would make it impossible to accept the fungus as having been definitely identified as *Blastomyces dermatitidis*. In the second case the statement was made that the organism gave the cultural characteristics of the genus *Cryptococcus*, thereby eliminating it from consideration as Gilchrist's organism. It is therefore clear that neither case can be accepted as an instance of North American blastomycosis.

Beregoft-Gillow expressed the view that it is absurd to think that mycotic diseases are a rarity in this country and stressed the need for teaching laboratory workers to recognize the various fungi. She also emphasized that trauma, ulcerations of various types, lesions of tuberculous or syphilitic origin and constitutional disorders, such as diabetes, are predisposing factors for the development of mycotic infections. Ferguson¹³ was quoted as stating that mycotic lesions of the lungs are as common as tuberculosis and that the two are often associated. However, Ferguson's statement was to the effect that pulmonary mycoses, especially moniliasis, were as common as tuberculosis in New Jersey. In her concluding remarks, the author claimed that the mycoses are easily cured by iodides, if treated early, a statement at variance with the views of nearly all authorities on Gilchrist's disease.

In 1939 an outstanding paper appeared under the joint authorship of Solway, Kohan and Pritzker¹⁴ from the Mount Sinai Hospital, Toronto, Canada. Their case was that of a 48 year old Italian fruit peddler, who commonly looked after his horse and attended to the chores around the stable. He had lived in Toronto for thirty-five years except for a short visit to Italy in 1914. In the early spring of 1938 his disease appeared with an insidious onset, characterized by cough, weakness and loss of weight from his maximum of 240 pounds (about 109 Kg) to 185 pounds (about 84 Kg). When first seen, on May 11, the observations included fever, shortness of breath, splenomegaly, hepatomegaly, a palpable mass involving the right epididymis, albuminuria and pyuria. The roentgenograms of the chest suggested miliary tuberculosis, though the individual lesions were somewhat larger and denser than usually seen in that disease. A tentative diagnosis of tuberculosis was made. On admission to the hospital on July 6, it was observed that a small rather innocent-appearing pustule had developed on the left ala nasi.

13 Ferguson, A. S. Blastomycosis of the Eye and Face Secondary to Lung Infection, *Brit. M. J.* **1** 442, 1928.

14 Solway, L. J., Kohan, M., and Pritzker, H. G. A Case of Disseminated Blastomycosis, *Canad. M. A. J.* **41** 331, 1939.

and that his prostate gland was enlarged. In addition, he had mild diabetes and there was evidence of arteriosclerotic retinopathy. The spleen was palpable 3 fingersbreadths below the costal margin, while the liver extended down below the umbilicus.

A roentgenogram of the spine revealed no abnormalities except for osteoarthritic changes, but an area of bone destruction was revealed on the anterior surface of the tibia, at the junction of the middle and lower thirds. The lesion on the nose gradually enlarged and, when incised, yielded only a few drops of oily-looking fluid. On July 21, weakness in the right leg developed, with loss of sensation to heat and cold and pain in the region of the inner border of the tibia. By the next day the left leg was also involved, and within two days transverse myelitis was fully developed, affecting motor, sensory and sphincteric functions. On July 23, the nasal mass and the right testis were removed. It was stated that blastomycetes were seen in both tissues, and positive cultures were obtained from pus in the epididymis and from a superficial pustule above the right ankle. On subculture the organism was identified as "*Zymonema dermatitidis*," a synonym for *B. dermatitidis*. Mice were inoculated and these organisms were recovered in three days from the peritoneal washings.

The histologist reported that the biopsy revealed areas of frank necrosis associated with polymorphonuclear leukocytes, and surrounding these lesions was a fibroblastic stroma in which were many giant cells. Spherical bodies with a refractile double-contoured shell, some in a budding stage, were visualized. The patient died on August 3, after a steady downhill course. Autopsy disclosed blastomycotic involvement of the lungs, skin, bone, spinal cord, prostate gland and epididymis. The enlarged liver and spleen showed only chronic hepatitis and splenitis of a nonspecific type. It was stressed that no involvement of the vertebrae was seen and that the transverse myelitis was due to direct invasion of the spinal cord itself. The authors claimed that this was only the third case on record of blastomycosis involving the cord. The mycologic studies in this case were conducted in the laboratory of the Department of Health of Ontario. Although the details of the cultural studies unfortunately were not reported, it would seem that this presentation warrants acceptance as at least a presumptive, if not a definitely proved, case of systemic Gilchrist's disease.

This analysis of the reports of North American blastomycosis emanating from Canada leads to the conclusion that only the cases of Shepherd and Rhea and of Solway, Kohan and Pritzker could be considered for inclusion in the category of proved cases, and even these outstanding publications were not entirely complete. Crich's case could be accepted as a presumptive one, but of all the rest only Gillies' re-

port and Primrose's first case might rate enrolment in this classification. In no instance, up to the time of writing, has any Canadian author utilized the specific intracutaneous test or complement fixation reaction. In addition, most reporters have failed to present complete details of the cultural studies to prove the identity of the organism. It is to be hoped that future reporters will benefit from these errors of omission and that shortly the Canadian literature will be enriched by a publication which presents all the evidence for an unequivocally proved diagnosis of North American blastomycosis.

REPORT OF A CASE

History—Mrs H. G., a 40 year old wife of a farmer, presented herself on May 3, 1943, with the complaint of pain above the right lower costal area, in the axillary region, with radiation anteriorly under the breast. The onset of the pain dated back three weeks. It had been constant, but varied considerably in intensity, at no time had it been acute. In the main it appeared to be a dull aching discomfort. It was aggravated slightly by twisting or bending movements and incessantly by deep inspiration. There were no other symptoms of any sort.

The past history was noncontributory. In fact, she had never had any significant illnesses or operations. She had, however, been treated for hypochromic microcytic anemia in 1938, which had responded readily to iron therapy. She had not been outside the environs of her community in many years. She had had 6 children, all of whom were living and well. Both parents were alive and in good health. Her only brother had died in infancy, but 2 sisters were in robust health, 1 of whom had made a good recovery from minimal pulmonary tuberculosis. One sister died at the age of 28 years from septicemia following a miscarriage.

Physical Examination—The initial examination revealed a well developed and well nourished white woman, with no objective evidence of ill health. Her height was 5 feet 4 inches (about 163 cm) and her weight 137 pounds (about 62 Kg). The temperature was 98 F, the pulse rate was 78, and respirations were 18. The head and neck were normal aside from two carious teeth. Lymphadenopathy was not present, the thyroid was not enlarged, and the breasts appeared normal. No abnormalities were noted incident to the examination of the cardiovascular system, lungs and abdomen. The systolic blood pressure registered 112 mm of mercury and the diastolic pressure 70. A hemoglobin estimation was observed to be 90 per cent, the Standard Kahn and Wassermann reactions of the blood were reported negative. The urine presented no abnormal observations at any time.

Clinical Course—One week later the patient reported that the pain still was present constantly, but inspiration no longer increased its intensity. She was unable to lie on the right side with any comfort, but the pain was not as annoying as previously. A positive reaction to a tuberculin patch test was obtained, but a roentgenogram of the chest revealed no abnormalities (fig 1). On June 4, 1943, she stated that the pain had not changed significantly. Roentgenographic investigation of the dorsal vertebrae was refused by the patient, as she wished to have a therapeutic trial of strapping of the chest. On June 15, she claimed that there had been great improvement effected and that she now experienced only incessant mild aching discomfort. She was convinced that the pain would shortly be

eradicated entirely, but promised to report for roentgenologic studies should the condition relapse. Her weight at that time was 133 pounds (about 60 Kg.)

Nothing further was heard from the patient until six months later. On December 14, she reappeared with the history that the pain had steadily progressed. She had undertaken a series of osteopathic treatments and was inclined to blame these manipulations for the fact that she had been confined to bed about half of the preceding two months.

The pain was still experienced in the right lower part of the chest, but was also noted in the lower portion of the neck. The intensity varied considerably, it might be severe for several days and then gradually improve, only to relapse

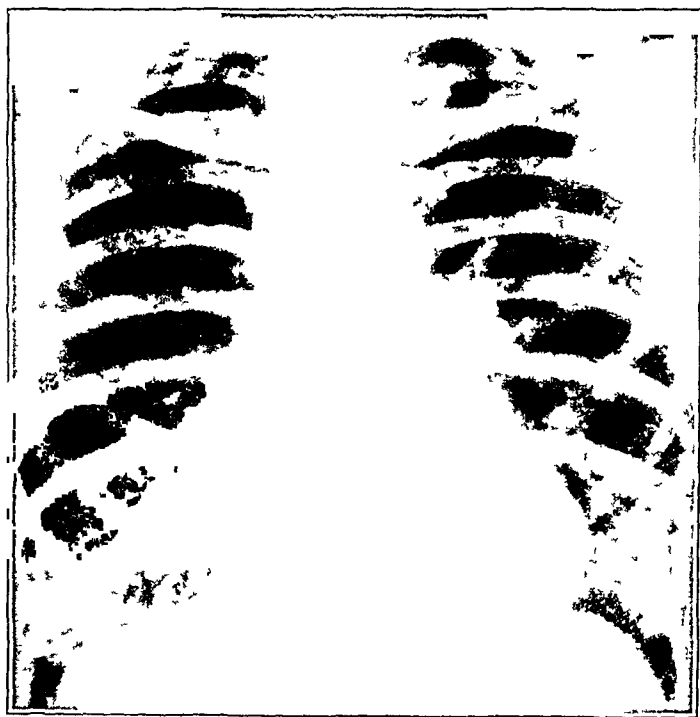


Fig 1—Roentgenogram of the chest, May 14, 1943. No lesion is evident.

She was now unable to lie on either side. The pain was aggravated by flexing the neck, and when it was severe she had found raising the arms from the shoulders almost impossible to accomplish. Picking up articles from the floor could be undertaken only by acutely flexing the knees without bending the back.

A roentgenogram (fig 2) revealed a destructive lesion, involving the fourth dorsal vertebra and the third to a much lesser extent. No abscess formation was evident. Consultation with a radiologist and an orthopedist resulted in a unanimous opinion that the lesion most probably represented metastatic malignant growth, with the site of the primary neoplasm undetermined. It was, however, felt that the lymphoblastomas and Pott's disease were not entirely excluded.

First Hospital Admission—On Jan 11, 1944, the patient was admitted to the public medical ward of the Ottawa Civic Hospital. Prolonged rest in bed, in a position of hyperextension of the spine, was advised by the orthopedic consultant. A second roentgenogram of the chest, on January 16, failed to reveal a definite lesion, although subsequent comparison of this picture with the initial one sug-

gested slightly increased linear detail in the upper lobe of the right lung. A gastrointestinal examination, with barium sulfate given rectally, likewise gave negative results. Repeated physical examinations failed to disclose the site of a primary neoplasm. Investigation of the pelvis, including a diagnostic curettage, threw no light on the problem.

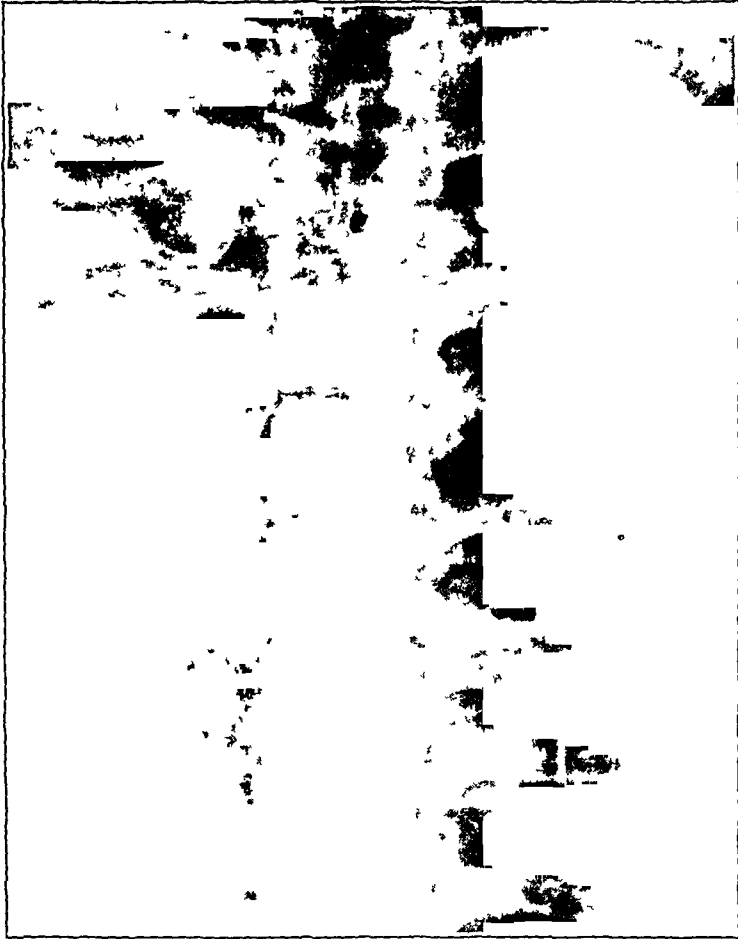


Fig 2—Roentgenogram of the spine, Dec 15, 1943, showing the destructive lesion involving the third and fourth dorsal vertebrae.

Early in March, almost eleven months after the onset of the illness, the patient complained of a slight cough for the first time and within ten days experienced slight hemoptysis. A few rales could then be heard in the right infraclavicular area. The third roentgenogram of the chest (fig 3), on March 11, revealed an extensive parenchymal lesion, involving the right upper lung field. On further inquiry at this time, the patient recalled having a "cold" in October 1943, which lasted only about one week, during which she remembered coughing up a little blood-tinged sputum. While the remarkable delay in the appearance of this pulmonary involvement gave rise to considerable discussion among the various members of the medical staff, it was considered that it probably represented an area of atelectasis secondary to a small bronchogenic carcinoma. During her time in the hospital, the patient had an irregular low grade fever, with the temperature usually ranging between 98 and 100 F, with occasional peaks of 101 or 102 F. The

pulse rate varied between 64 and 96 beats per minute and the respiratory rate between 16 and 22

Numerous examinations of the sputum failed to reveal tubercle bacilli, but mixed bacterial flora were commonly reported, with *Micrococcus catarrhalis* and *Streptococcus viridans* predominating. Fungi were never identified, but a request for a specific search for them, to include special cultures, was not made. The erythrocyte count was 5,090,000, with a hemoglobin level of 130 Gm and a leukocyte count of 11,450. The blood sedimentation rate showed a fall in one hour of 44 mm. Estimation of the serum alkaline phosphatase was 4.4 units.

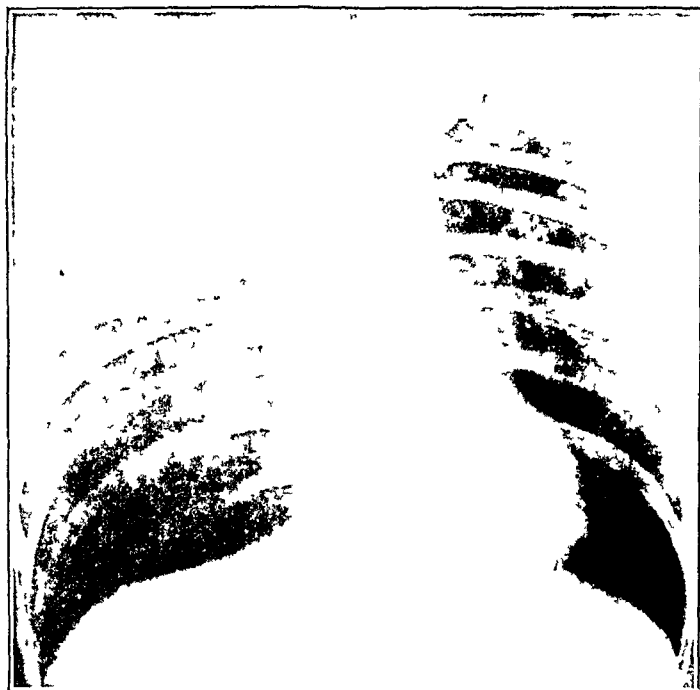


Fig 3—Roentgenogram of the chest, March 11, 1943, showing extensive parenchymal infiltration in the right upper lung field

Early in April 1944, pain and slight swelling were noted about the right elbow region and a suggestion of erythema about the left ankle. The patient's general condition deteriorated only gradually during her first admission to the hospital, which terminated on May 9, at her urgent request, as she wished to spend the summer months at her residence.

On August 16, she was again examined at her farm home, about 20 miles outside the city. It was then observed that the spinal pain had subsided, but she was greatly distressed by granulomatous ulcerations in the region of the right elbow and both ankles, which had developed shortly after her discharge from the hospital.

Second Hospital Admission—The patient was readmitted to the hospital on November 2. By this time she was suffering acute pain and was obviously cachectic. She had considerable pain in both sides of the chest, which often felt as if it were encircled by a vise. Administration of morphine was essential prior to dressing the granulomatous ulcers, which were large and deep, exposing the underlying structures. She was febrile as before, and the pulse rate

varied between 100 and 140 per minute, with a respiratory rate of 24 to 30. The red blood cell count was 4,010,000, with a hemoglobin content of 9.8 Gm and a leukocyte count of 22,850. A differential white cell count revealed the following percentages: single-lobed neutrophils 34, multilobed neutrophils 46, basophils 1, eosinophils 1, lymphocytes 9 and monocytes 9. Cultures from the granulomatous areas grew a nonhemolytic *Staph aureus*. The urine revealed only a faint trace of albumin and presented no Bence-Jones proteins.



Fig 4—Roentgenogram of the right elbow, showing the osteolytic lesion involving the humerus, radius and ulna

A roentgenogram of the chest revealed the lesion in the right lung as before, but it was definitely smaller in size. Roentgenograms of the spine disclosed a further extension of the osteolytic process in the dorsal vertebrae. The body of the fourth dorsal vertebra was practically entirely destroyed, producing considerable kyphosis with angulation of the spine at this level. Decided destruction of the margins of the third dorsal vertebra and moderate involvement of the upper portion of the fifth, with slight damage to the second and sixth dorsal vertebrae, were also noted. Considerable destruction of the posterior arc of the right fourth rib was evident, extending out from the spine for a distance of about 3 inches (about 7.5 cm). A few small mottled areas of demineralization were visible

about the upper portion of each femur and to a slight extent in the lower half of the pelvis. Similarly, roentgenograms revealed irregular mottled decalcification involving the lower ends of the left tibia and fibula. Slight involvement of the left astragalus, the tarsals and metatarsals was also evident. The articular surfaces of the left ankle joint had almost disappeared. A study of the right elbow area (fig 4) uncovered a mottled osteolytic lesion, the size of a quarter, involving the lower end of the right humerus, with similar involvement of the upper end of the radius and a much larger area of destruction of the upper portion of the ulna.

Numerous consultants examined the patient at various times, but, without exception, all subscribed to the opinion that the osseous lesions represented metastases from a primary bronchogenic carcinoma. The granulomatous ulcerative lesions of the skin and subcutaneous tissues did give rise to some misgiving, but only the dermatologist considered the possibility of mycotic infection. Unfortunately, fungi were not identified in direct smears of the material obtained from one of these lesions, and cultural studies were not requested. It was subsequently regretted, of course, that a biopsy had not been undertaken.

Following the patient's death, on December 10, an autopsy was performed. The following description was abstracted from the pathologist's report:

Summary of Gross Postmortem Observations—The body was that of an emaciated and cachectic white woman, estimated to weigh 100 pounds (about 45 Kg) and appearing to be approximately 40 years of age. The head and neck were not remarkable, while the chest was symmetric and the abdomen scaphoid. The skin of the entire body was excessively pale, loose and somewhat inelastic. A large irregular sloughing ulcer involved the lower third of the right arm and the upper third of the forearm. The margins of the ulcer were slightly heaped up and granular, while the base was covered with foul-smelling necrotic debris. The lesion had deeply penetrated the underlying soft tissue, exposing the capsule of the elbow joint, adjacent to which were ragged areas of bone destruction, involving the radius, ulna and lower end of the humerus. Similar, though smaller, lesions were present on both ankle joints, these ulcers also extended into and involved the regional osseous and articular structures. Apart from a walnut-sized soft node palpable in the right axilla there was no evidence of generalized enlargement of lymph nodes.

Thoracic Cavity The thoracic viscera lay in their usual positions, and the thin straw-colored fluid which was present in the pleural spaces and pericardial sac was not excessive. The left pleural space was free from adhesions, while the apical third of the right lung was intimately bound to the paravertebral gutter by unusually dense firm whitish scar tissue, which could be separated only by sharp dissection. There was no shifting of the mediastinum, and the heart in situ was normal in size and shape. The mediastinal lymph nodes were not significantly altered and showed only a moderate amount of anthracosis.

Heart The heart, which weighed 340 Gm, was normal in size and shape. The valve orifices were normal in circumference and the cusps thin, pliable and translucent. The myocardium was firm, but slightly paler than usual. The coronary arteries were patent throughout and showed only a negligible degree of intimal fatty streaking.

Lungs The left lung was clothed by pale, smooth and glistening serosa and was soft, pillowy and crepitant on palpation. The cut surface was retracted, dry and salmon pink. No areas of consolidation were demonstrable. The bronchi, peribronchial lymph nodes and intrapulmonary vessels were normal.

The middle and lower lobes of the right lung were likewise normal, resembling in all respects those on the opposite side. The upper lobe of the right lung was considerably altered. The upper third of this lobe was represented by an extremely firm dense creamy white rubbery mass, resembling old fibrous scar tissue. This mass was continuous with a fibrosing process which involved the right lateral aspect of the adjacent upper four thoracic vertebrae. On section the apical portion of this lung was observed to be occupied by a small elongated ragged cavity, lined by greenish gray necrotic debris. This cavity communicated

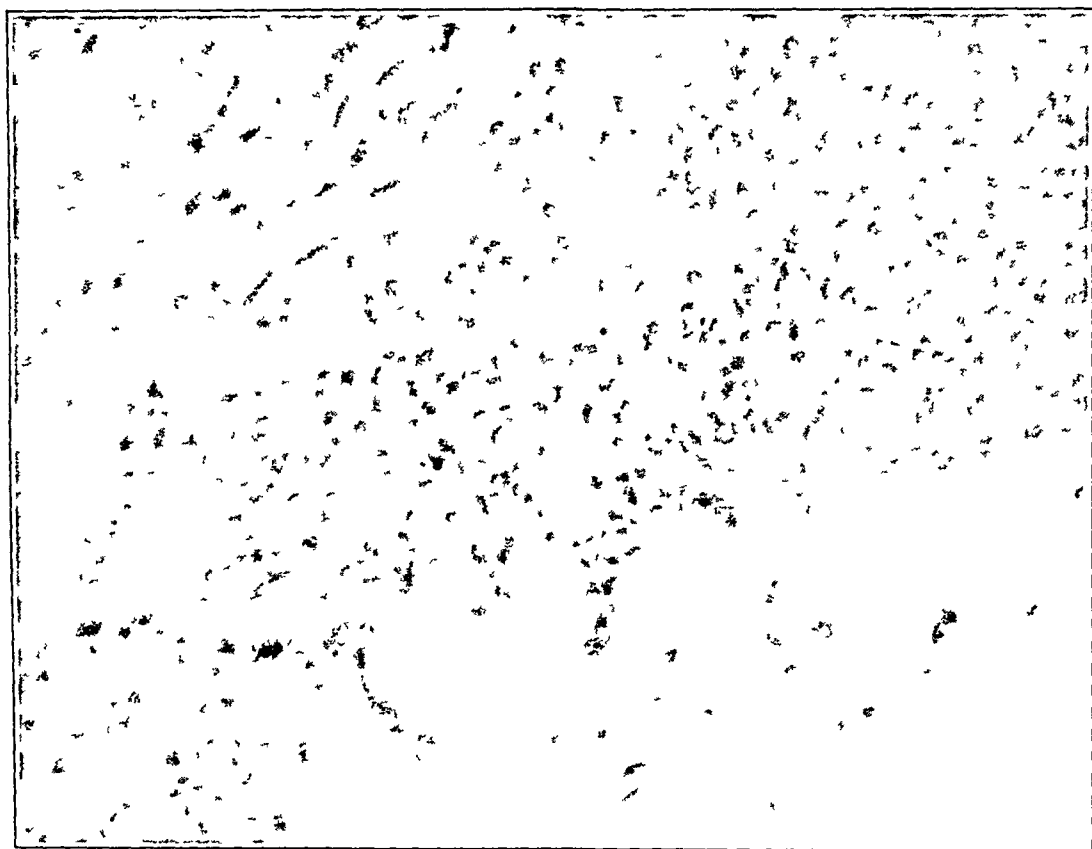


Fig 5—Low power photomicrograph of the wall and lining of the pulmonary abscess, showing myriads of the blastomycetes in the areas adjacent to the cavity (hematoxylin and eosin $\times 130$)

with the main bronchus to this lobe via one of its tertiary ramifications. The parenchyma of the lower portion of the upper lobe was slightly indurated, but was sharply demarcated from the dense scar tissue surrounding the cavity previously described.

Abdominal Cavity and Viscera The abdominal viscera lay in their usual positions, and no excess of fluid was present. The peritoneal surfaces were all smooth and glistening. No gross lesions were demonstrable in the liver, spleen, kidneys, adrenal glands, pancreas or pelvic organs.

Osseous System As mentioned previously, the right lateral aspect of the bodies of the four upper thoracic vertebrae were in direct continuity with the scarlike lesion involving the apex of the lung on the same side. It was apparent that these structures were involved by a progressively destructive and fibrosing process, much of the bone being replaced by creamy or pearly white rubbery scar

tissue, throughout which were small pockets containing putty-like necrotic material. This was particularly apparent in the region of a compression fracture which involved the second thoracic body.

A similar destructive lesion was observed to involve the coronoid process of the right ulna with destruction of the bone and replacement by dense fibrous material containing necrotic foci of similar putty-like material. A pathologic fracture had occurred at this site also.

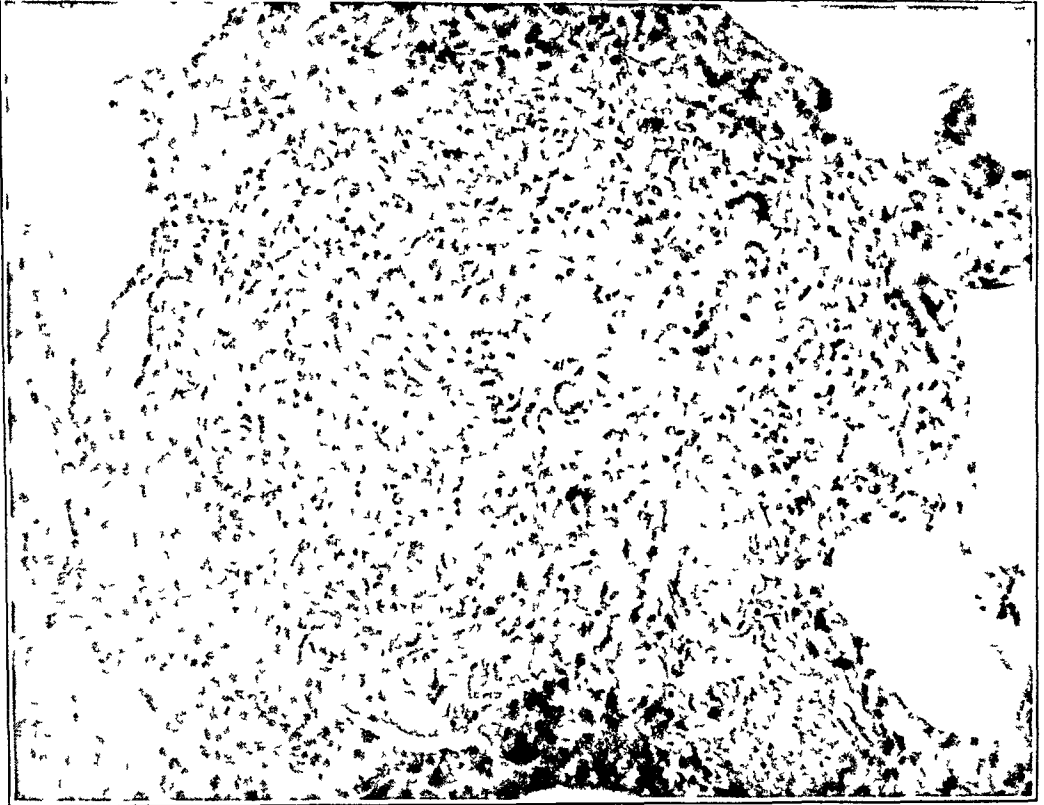


Fig 6—Early tubercle-like lesion in the lung, showing fibrous proliferation, giant cells, lymphocytic infiltration and a few blastomycetes (hematoxylin and eosin $\times 130$)

Histologic Changes Numerous sections from all the grossly demonstrable lesions were examined, in addition to sections from the heart, left lung, liver, spleen, kidney, adrenal glands, pancreas, uterus, ovaries and thyroid, with the exception of the spleen the microscopic picture of the latter viscera was within normal limits.

It was evident that the pathologic processes represented by the lesion in the apex of the right lung, the adjacent vertebral bodies, the cutaneous ulcers and the regional osseous structures were of an essentially similar type. In addition to the routine hematoxylin and eosin stain and iron hematoxylin stain, sections from selected areas, stained by Glynn's modification of Gram's method for bacteria, and other sections stained specifically for acid-fast organisms were studied. The most characteristic picture was obtained from a study of the pulmonary lesion (figs 5, 6, 7, 8 and 9). Here the cavity, described previously, which was devoid of

contents, was seen to be lined by granulomatous material consisting of proliferating fibroblasts together with a few capillaries

This granulation tissue was heavily infiltrated with large numbers of lymphocytes, as well as a few scattered plasma cells. Present throughout the more superficial layers, that is, in the immediate vicinity of the cavity itself, were large numbers of peculiar bodies. These were rounded structures, varying from approximately 8 to 20 microns in size and possessed of a highly refractile membrane. The nucleus in most instances was rounded in form and fairly homogeneous,

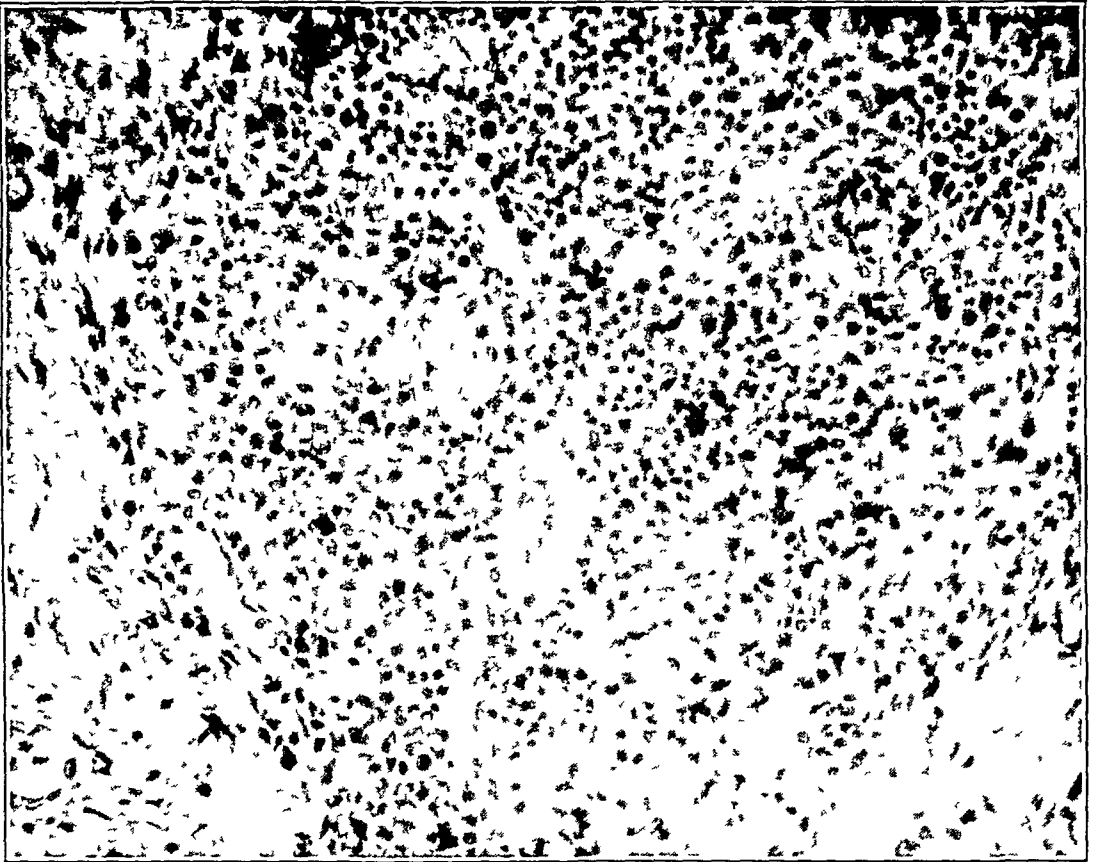


Fig 7—Early inflammatory reaction in the lung. The infiltrate is predominantly lymphoid. Alveolar structures have been destroyed, but bronchioles still persist (hematoxylin and eosin $\times 130$)

though in some cases it was compressed and displaced to the periphery of the cell, thus producing a "signet ring" appearance. A careful search showed many of these bodies to possess single buds, the development of which could be traced into the formation of similar daughter cells (fig 10). These bodies, which tended to occur in clusters, were interpreted as being typical of the fungus responsible for blastomycosis dermatitidis.

Peripherally this granulomatous zone merged rapidly into an area characterized by the formation of extremely dense relatively acellular hyalin-like material, the arrangement of which tended to maintain the ghostlike outlines of preexisting structures, such as vessels, bronchi and alveoli. The interstices of this scarlike tissue were infiltrated by numbers of lymphocytes and here and there large multinucleated giant cells, which in some instances contained the

pathogenic bodies previously described in varying stages of degeneration. In other areas, the destruction of the parenchyma was not complete and distorted bronchioles could be identified surrounded by a dense halo of lymphocytic cells. Sections taken from the lungs adjacent to the area of massive scarring showed a few extremely early satellite lesions. These were characterized by a rounded conglomeration of fibroblasts, moderately heavily infiltrated with lymphocytes,

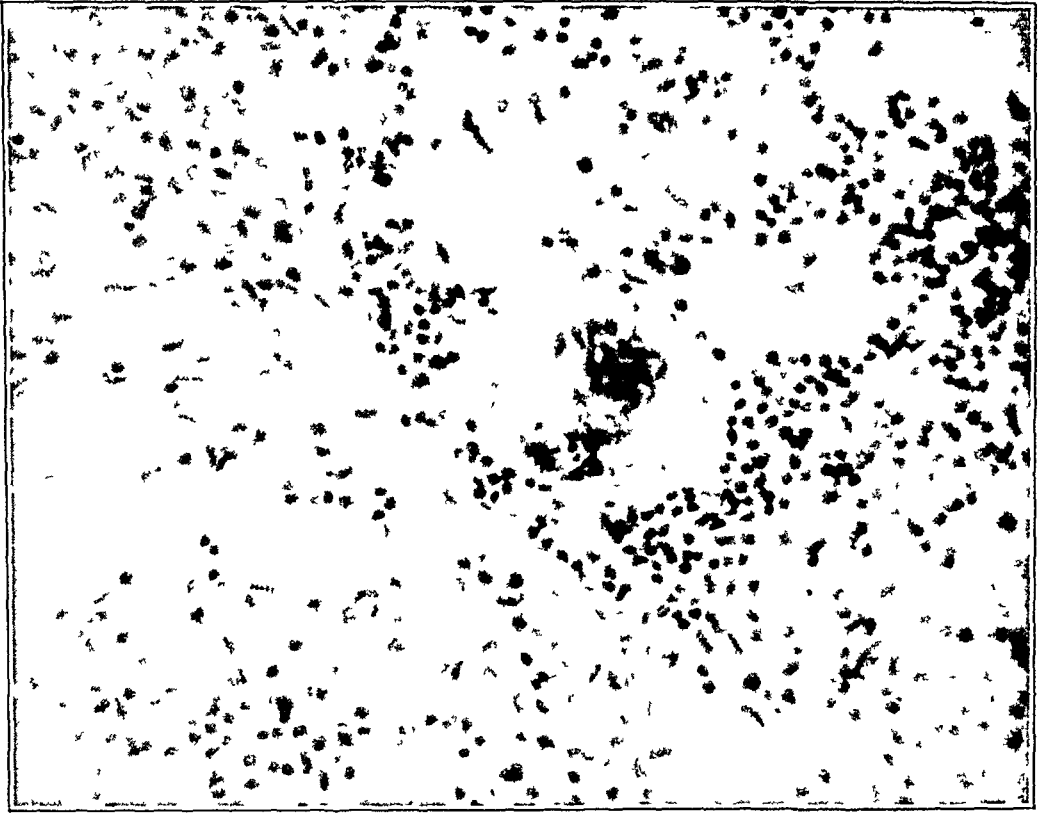


Fig 8—Early scar in the lung. Lymphocytes and giant cells still persist, but no blastomycetes were present in such areas (hematoxylin and eosin $\times 130$)

containing a few multinucleated giant cells, while, lying in the interstices or within the body of the giant cells, parasitic bodies could be identified.

Sections of bone revealed an essentially similar picture. Scattered areas of necrosis were encountered, this being of a fairly homogeneous bland almost caseous type. These necrotic foci were margined by cellular granulations in which the blastomycotic bodies were to be seen (fig 11). The process had extended through the cortical bone and had destroyed much of the medullary tissue of the vertebral bodies. The medulla of the radius was more extensively involved than the cortex, and the impression was gained that the lesion at this site was intrinsic in origin.

Unfortunately, no epidermis was included in the sections of the cutaneous ulcers. The base of the ulcers, however, was seen to consist of extremely dense scar tissue studded with multiple necrotic foci undergoing granulomatous organization, varying numbers of the parasitic structures being present throughout the latter.

One section of spleen revealed the presence of a single minute necrotic focus, surrounded by an extremely dense hyalin capsule, infiltrated with lymphocytes and containing a few multinucleated giant cells in which the blastomycetes were demonstrated (fig 12)

It is worthy of note that it was extremely difficult to demonstrate the pathogenic structures apart from areas of necrosis or, in the lung, gross cavitation

Pathologic Diagnosis The diagnosis was blastomycosis of lungs, bone and skin

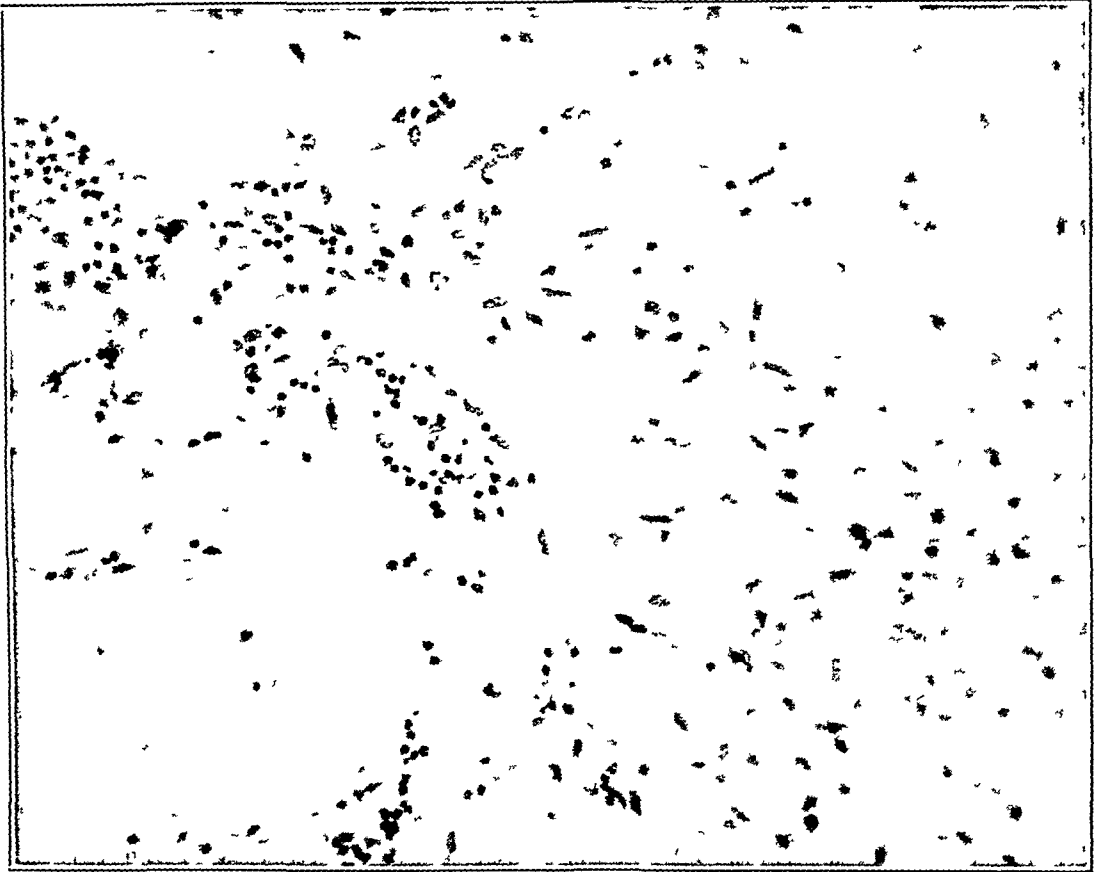


Fig 9—Late pulmonary scar. Inflammatory cells have disappeared, and the tissue is assuming a dense acellular hyaline appearance (hematoxylin and eosin $\times 130$)

COMMENT

The investigation of this case fell far from establishing the correct diagnosis prior to autopsy. In retrospect it is obvious that the primary mistake was the same one stressed by many authors—failure to give the mycoses their proper place in the differential diagnosis of osseous and pulmonary lesions of obscure causation. However, it would not have been possible to make the diagnosis until there were manifestations in the lungs, which were not evident until after ten months from the onset of the illness. At this point of failure to have the sputum

subjected to cultural studies for fungi was the first serious error. When the granulomatous ulcerative lesions of the skin appeared, the true nature of the disease should have been suspected. Neglecting to have cultural studies, animal inoculations and biopsies of the cutaneous lesions constituted the second major mistake. The third

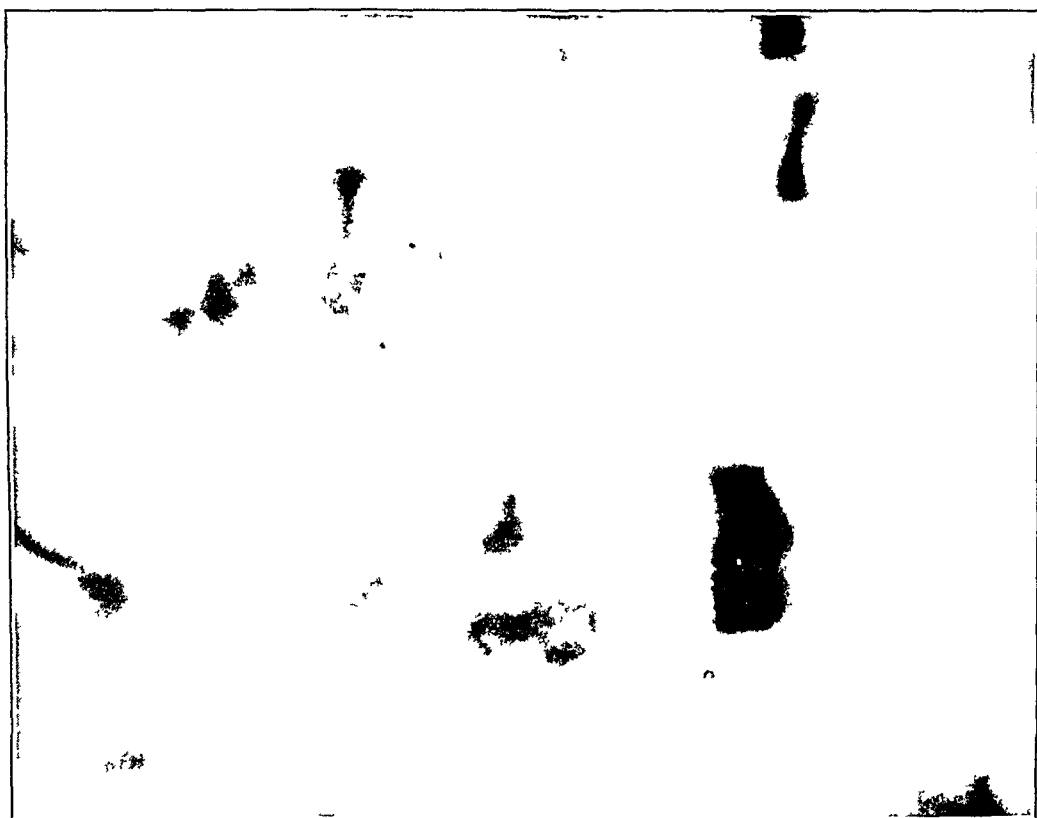


Fig 10—Section from necrotic pulmonary tissue. Several diastomycetes can be seen in the central portion of the field in various stages of budding (hematoxylin and eosin $\times 1300$)

major error of omission concerned the fact that the specific intradermal test and the complement fixation serologic test were never carried out. The utilization of these aids at any time during the progress of the case would have pointed the way, almost certainly, toward the proper diagnosis. All of these regrettable errors were due directly to the one common factor—the mycoses were never seriously considered in the differential diagnosis.

Unfortunately, it fell to the lot of the physician performing the autopsy to be the victim of the fourth gross mistake, inasmuch as cultural studies of the fungi identified in the tissues were not conducted. As a consequence, it is impossible to classify the disease in this case.

as an unequivocally proved example of Gilchrist's disease. However, the demonstration of the typical single-budding organisms in the tissues, in conjunction with the clinical features, would seem to be adequate evidence to warrant a presumptive diagnosis of North American blastomycosis.

The case history was somewhat unusual in the fact that it has been impossible to find a previously published report wherein the disease

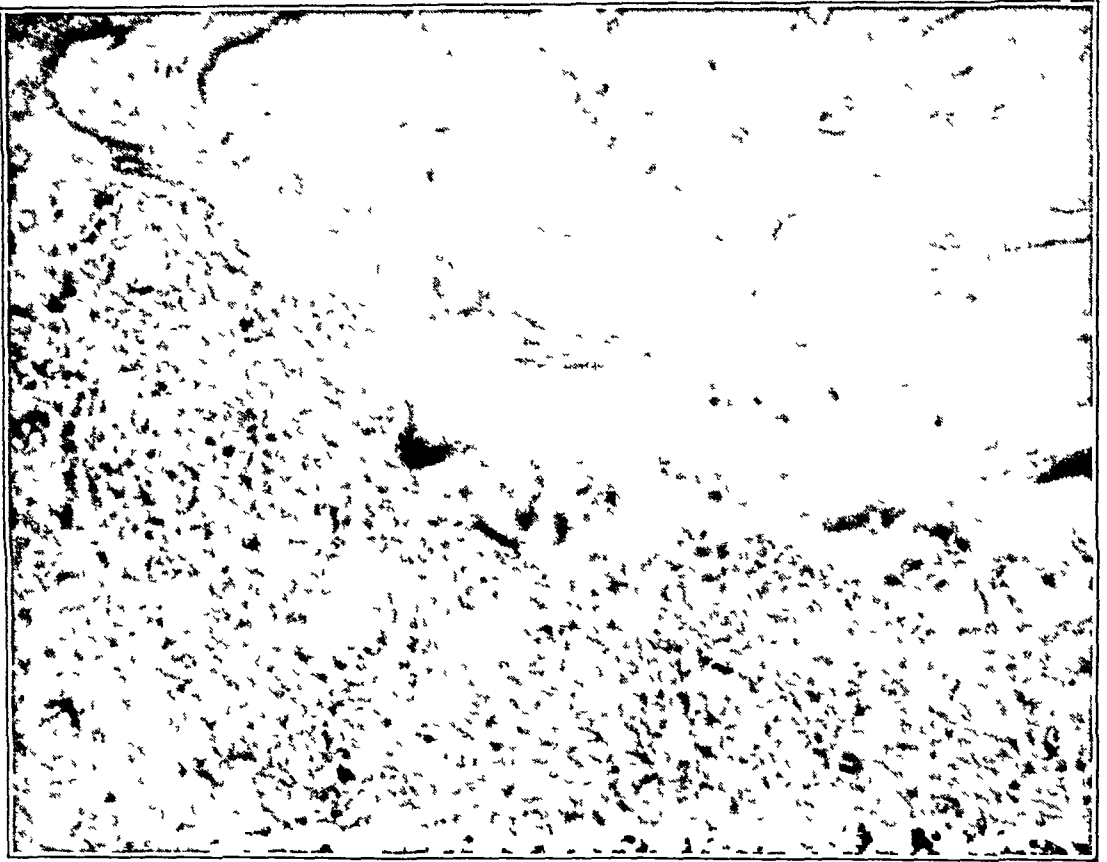


Fig 11—Blastomycotic process encroaching on and destroying the vertebral cortex. Unusually large numbers of blastomycetes, many budding, are readily seen (hematoxylin and eosin $\times 130$).

manifested itself with root pain as the first complaint, though pain in the chest is accepted as a common symptom. Inability to demonstrate the pulmonary lesion for such a long time after the onset made the problem more confusing, and this was a significant factor in the erroneous conclusion that the destructive lesion of the dorsal vertebrae represented a metastatic neoplasm. This error is in contrast with the usual mistake of considering tuberculosis as the likely diagnosis. It seems extremely probable that the primary lesion in this case did originate in the lung, but owing to its location in that portion of the pul-

monary apex which lies in the paravertebral gutter, the original small focus was not visualized on the initial roentgenograms

CONCLUSIONS

This case serves to emphasize once more the necessity for suspecting the mycoses in pulmonary and osseous lesions when the diagnosis has not been established with certainty and especially when pulmonary, osseous and cutaneous lesions coexist

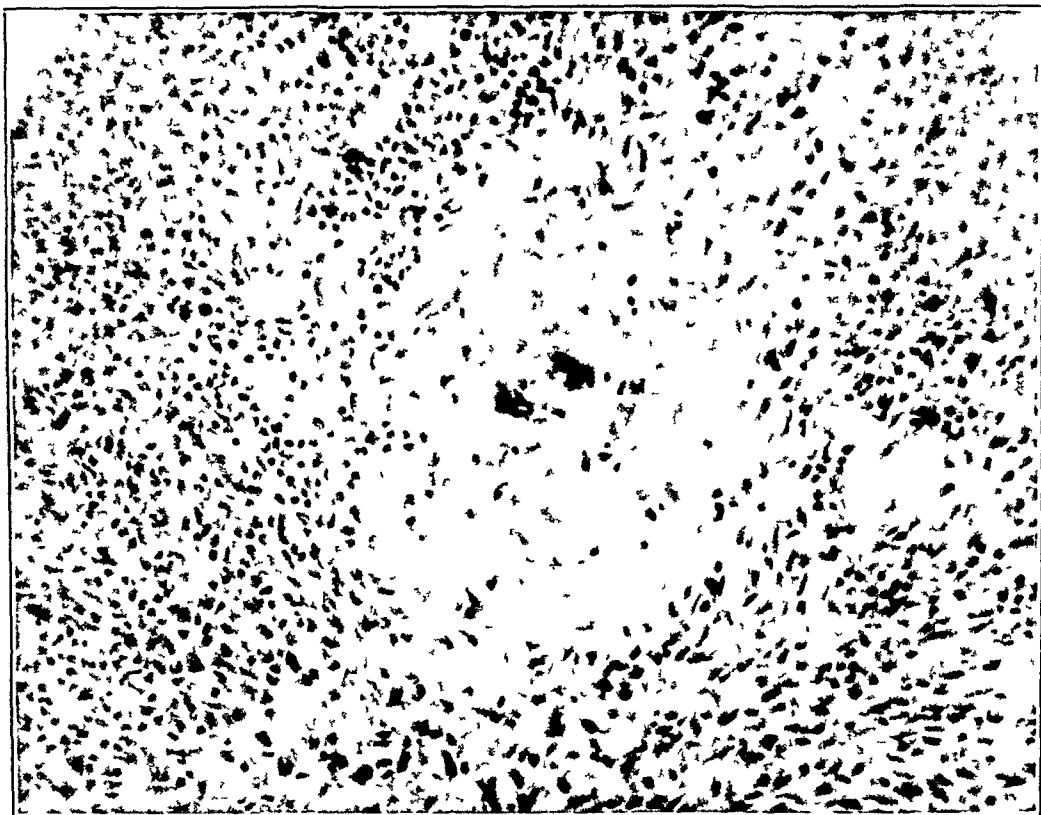


Fig 12—Solitary splenic lesion, resembling a fibrosed tubercle, with two central multinucleated giant cells (hematoxylin and eosin $\times 130$)

It seems clear that the sputum of many patients with pulmonary disease should be subjected to special cultural studies for fungi. In addition, it would appear certain that the complement fixation test and the cutaneous test should become a necessary part of the investigation of obscure pulmonary and osseous diseases. Interesting information might be uncovered by studies conducted in tuberculosis sanatoriums utilizing these tests in all cases in which repeated search has failed to demonstrate tubercle bacilli.

SUMMARY

A critical analysis of all reports of Canadian cases of North American blastomycosis is presented

Another report of a case of the disseminated disease from Canada is added to the literature

263 Somerset Street West

COMPARATIVE TIME ACTION OF GLOBIN INSULINS

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AND

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THERE has been constant and increasing interest in the time action of modified insulins in the search for an ideal preparation capable of providing good control for the greatest number of diabetic patients by a single daily injection. The introduction of protamine insulin by Hagedorn¹ in 1936 was a major contribution, and in a large number of cases the diabetes is satisfactorily controlled with single daily injections of protamine zinc insulin. However, it is evident that its time action is too prolonged for ideal purposes. Postprandial glycosuria and nocturnal reactions occur in many patients, particularly those with severe grades of diabetes. The need for an insulin with activity intermediate between that of regular insulin and that of protamine zinc insulin led to the development of globin insulin with zinc in 1939 by Reiner, Searle and Lang.² This product has also been referred to as globin zinc insulin and is commonly called globin insulin, the latter term is used in this paper for simplicity, with the understanding that zinc is always present. Mixtures³ of regular insulin and protamine zinc insulin also have come into common use. Mixtures containing two to three times as much insulin as protamine zinc insulin have been particularly efficient in the treatment of severe diabetes.

Aided by a grant from Burroughs-Wellcome & Co (U S A), Inc

From the Diabetic Service of Wesley Memorial Hospital and the Northwestern University Medical School, Department of Medicine

1 Hagedorn, H C , Jensen, B N , Krarup, N B , and Wodstrup, I. Protamine Insulinate, *J A M A* **106** 177-180 (Jan 18) 1936

2 Reiner, L , Searle, D S , and Lang, E H. On Hypoglycemic Activity of Globin Insulin, *J Pharmacol & Exper Therap* **67** 330-340 (Nov) 1939

3 (a) Colwell, A R , and Izzo, J L. Protamine Zinc Insulin Modified for Accelerated Action, *J A M A* **122** 1231-1236 (Aug 28) 1943. (b) Colwell, A R. Nature and Time Action of Modifications of Protamine Zinc Insulin, *Arch Int Med* **74** 331-345 (Nov) 1944. (c) Peck, F B , and Schechter, J S. Newer Insulin Mixtures. Follow-Up Study, *Proc Am Diabetes A* (1944) **4** 57-86, 1945

Globin insulin has been reported⁴ to control the disease in a greater number of cases than protamine zinc insulin. Some observers⁵ assert, however, that the action of globin insulin is too rapid, that it shows too great a tendency to cause afternoon reactions and that it permits too little overlapping in effect for best results in treatment of severe diabetes.

This investigation therefore was undertaken to determine the time action of standard⁶ globin insulin and to compare it with ordinary insulin and with protamine zinc insulin. The comparisons were made by obtaining many blood sugar curves and urinary sugar curves showing the action of single doses of the same size in well stabilized patients with diabetes mellitus. The possibility of altering the characteristic time action of globin insulin by varying its globin content was also investigated by the same method of comparison.

METHOD

Time action curves were determined by a method^{3b} previously used in studies of other insulins. Two patients with diabetes mellitus of moderate severity were given weighed meals every four hours day and night. Glucose values of the meals were adjusted to compensate for diurnal fluctuation in the amount of sugar in the blood and urine after constant and stable hyperglycemia and fractional glycosuria had returned and were maintained at preinsulin control levels for at least twenty-four hours. Single 60 unit doses of insulin were given. The concentration of blood sugar was determined by the method of Folin and Wu and that of the urine sugar by the method of Folin and Berglund. From two to twelve curves were obtained for each insulin studied.

A series of clear globin zinc insulins containing 38, 76, 190 and 380 mg of globin per hundred units of insulin was prepared by the method outlined by the Food and Drug Administration in the Federal Register.⁷ A 5 per cent solution of globin hydrochloride powder was slowly neutralized with sodium hydroxide solution. Most of the denatured protein was removed by centrifugation and filtration. Its native globin content was determined by nitrogen assay. Native globin solution, insulin containing 160 units per cubic centimeter and a solution of zinc chloride were then mixed in the proportions necessary to obtain the globin contents mentioned. Zinc content was kept constant in this series of insulin preparations at 0.3 mg per hundred units of insulin. The pH was adjusted to

4 (a) Roberts, J. T., and Yater, W. M. Comparison of the Clinical Use of Protamine Zinc Insulin and Globin Insulin in Equal Doses, *Ann Int Med* **26** 41-66 (Jan.) 1947. (b) Sindoni, A., Jr. Fasting Blood Sugar vs Postprandial Blood Sugar as Observed in Normal Individuals, Medical (Non-Diabetic) Patients, and Patients with Diabetes, *Am J Digest Dis* **13** 178-192 (June) 1946.

5 (a) Peck, F. B. Insulin Mixtures and Modifications, *M Clin North America* **31** 343-357 (March) 1947. (b) Protas, M. Comparative Study of Action of Globin Insulin with Other Forms of Insulin, *M Ann District of Columbia* **13** 254-257 (July) 1944. Colwell.^{3b}

6 Globin Insulin with Zinc, supplied by Burroughs Wellcome & Co. (U. S. A.), Inc., New York.

7 Fed Register **8**:11837 (Aug 27) 1943.

between 34 and 38. Insulin containing 19 mg of globin per hundred units was prepared by mixing standard globin insulin and regular insulin in equal parts. This makes a clear insulin containing half as much globin and zinc as standard globin insulin.

Chart 1 shows the method of calculation used to express composite time action curves in terms of percentage of average control period values before insulin was

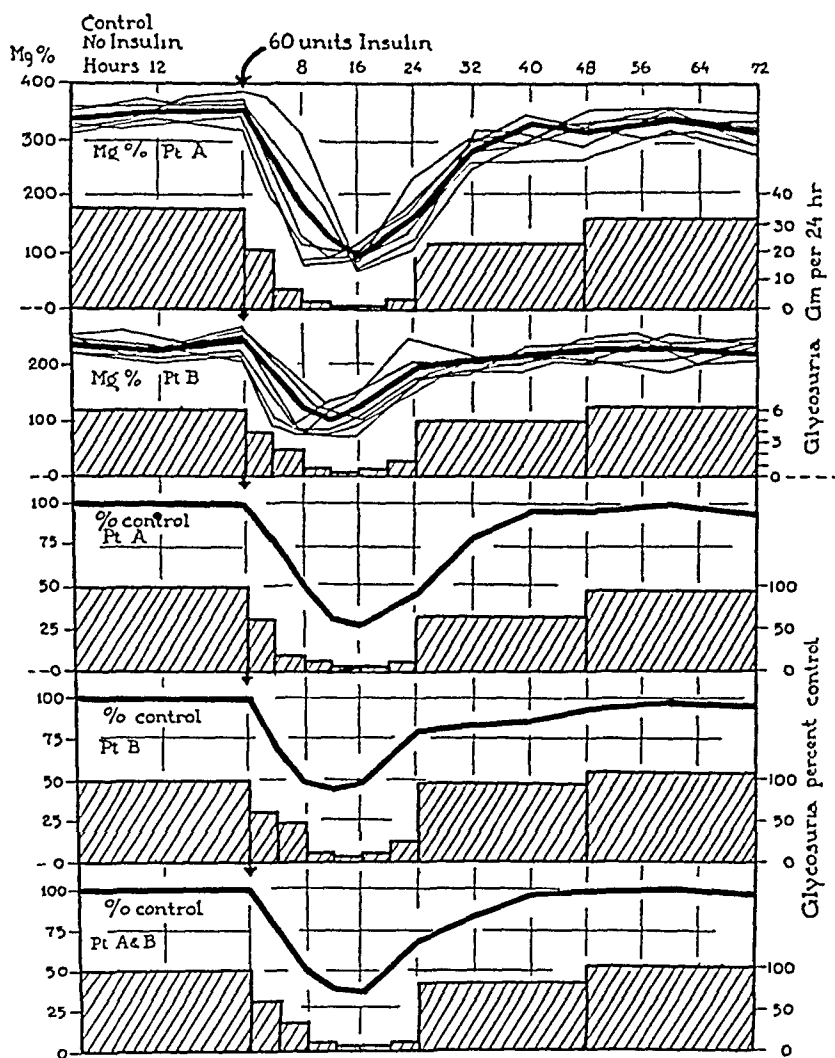


Chart 1—Time action of standard globin insulin, showing method of calculation to express a composite time action curve as average percentage of average control period.

given. The fine lines in the upper graph show the individual actual blood sugar curves for 1 patient receiving standard globin insulin. The heavy line represents the average of these values. The average concentrations of urine sugar are shown in grams per twenty-four hours. Data for curves on the other patient are shown in the same manner in the second graph. These average values were then recalculated in percentage of those for the twenty-four hour preinsulin control period and are shown for each patient in the third and fourth graphs. These percentage curves

for the 2 patients were then averaged, and a final composite curve, considered to represent the time action of the insulin studied (in this instance standard globin insulin), was obtained, as shown in the lowest graph. The same method of calculation was used for each insulin studied, all curves shown subsequently representing composite values obtained by such averaging. Insulin effect or activity was considered to be present when there was a reduction of 10 per cent or more in average values below preinsulin control levels.

RESULTS

Chart 2 shows the composite time action curve for standard globin insulin compared with those for regular insulin and protamine zinc insulin. The globin insulin curve is the composite of six individual curves for patient *A* and six for patient *B*, the regular insulin curve is

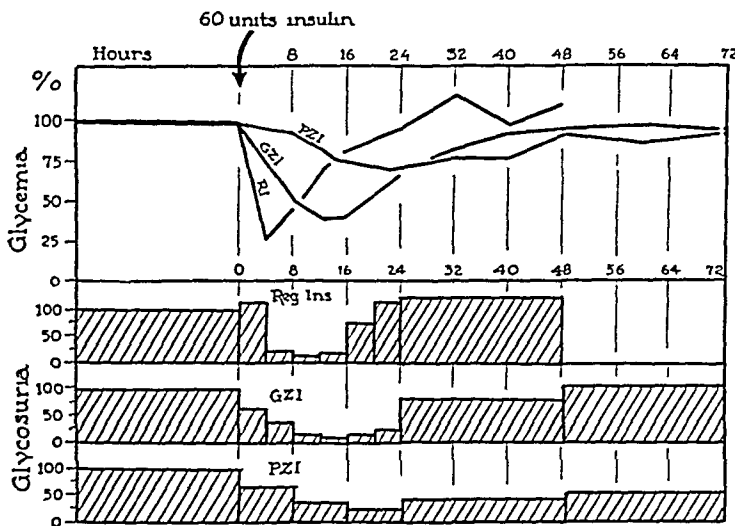


Chart 2—Time action of standard globin insulin compared with regular insulin and protamine zinc insulin

a composite of two curves for patient *B* and one for patient *A*. The protamine zinc insulin curve likewise combines three curves obtained for patient *A* and five curves for patient *B*.

Globin insulin showed a prompt effect in reduction of hyperglycemia to 72 per cent of the control level in the first four hours. The maximum effect occurred in from eight to sixteen hours, on the average, after which it diminished, with hyperglycemia rising to the control levels at about thirty-two hours. Prompt reduction in the urine sugar level of the first four hours to 65 per cent of the control level occurred, with maximum reduction of glycosuria in eight to twenty hours. There was slight reduction in the glycosuria of the second day.

The action of standard globin insulin, therefore, is seen to be intermediate between that of regular insulin and that of protamine zinc

insulin It is less intense, less prompt and more prolonged than that of regular insulin, but it is more rapid, much more intense and less sustained than that of protamine zinc insulin Prompt reduction of hyperglycemia with maximum effect at four hours was characteristic of the action of regular insulin, after which it rapidly rose to the preinsulin control level The glycosuria also returned to its control level in the middle of the

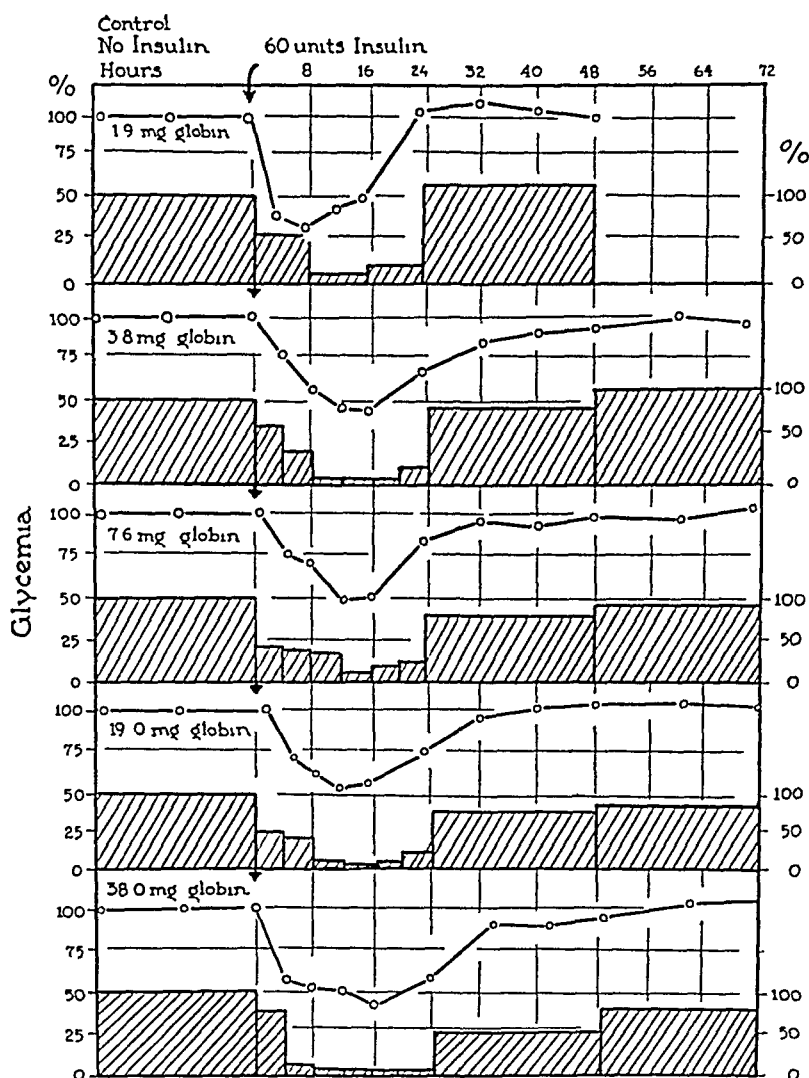


Chart 3—Effect of variation of globin content on time action of globin insulin

first day Protamine zinc insulin had a gradual onset of effect, with maximum intensity at twenty-four hours The effect persisted into the third day, as shown by both the blood sugar curves and the urine sugar curves

Chart 3 shows the effect of variations in the globin content on the time action of clear globin insulin A preparation containing 19 mg of

globin per hundred units of insulin acted more promptly and more intensely and was less sustained in effect than standard globin insulin containing twice as much globin. However, it was less intense and more prolonged in action than regular insulin. No second day effect was apparent.

As shown in the lower three graphs in figure 3, globin insulin preparations containing 7.6, 19 and 38 mg of globin per hundred units of insulin (from two to ten times the amount contained in the standard preparation) were not different in effect from the standard globin insulin containing 3.8 mg of globin per hundred units. It must be realized, of course, that these preparations containing larger amounts of globin were, like the standard preparation, clear preparations maintained in solution by adjustment of the pH to 3.4 to 3.8. Probably precipitated globin insulins with longer action could be prepared, if that were desirable. In fact, we have obtained some data, not related here, which show that precipitation alters the time activity of clear globin insulin.

COMMENT

The time action of globin insulin undoubtedly is intermediate between that of regular and that of protamine zinc insulin. There is some second day action when it is given in 60 unit doses to patients with moderate diabetes, as shown by reduction of the blood sugar levels at twenty-four hours and the urine sugar levels after twenty-four hours below the control values obtained without the use of insulin.

Bailey and Marble⁸ have reported results similar to ours in fasting diabetic patients. However, other reports have varied, particularly as to the duration of insulin effect. Sindoni^{4b} reported the observance of initial effect in two to three and one-half hours, with maximum effect at eight and one-half hours and a twenty-three hour effect which resulted in a sugar content well below the preinsulin level. Duncan and Barnes⁹ reported maximum daytime effect from morning doses, which faded at night. Martin, Simonsen and Homan¹⁰ reported insulin activity between midnight and 8 a.m. after morning injections in 11 of

8 Bailey, C. C., and Marble, A. Histone Zinc Insulin, Globin (Zinc) Insulin and Clear Protamine Zinc Insulin. Comparative Study of Their Action, *J. A. M. A.* **118** 683-690 (Feb. 28) 1942.

9 Duncan, G. G., and Barnes, C. A. Action of Globin Insulin Compared with That of Crystalline, Unmodified and Protamine Zinc Insulin, *Am. J. M. Sc.* **202**, 553-563 (Oct.) 1941.

10 Martin, H. E., Simonsen, D. G., and Homan, N. H. Time Activity Curves of Globin Insulin with Clinical Applications, *Am. J. M. Sc.* **208** 321-332 (Sept.) 1944.

30 patients Mosenthal¹¹ reported insulin effect in two hours, with a sixteen to twenty-four hour duration Protas^{5b} stated the belief that there is ordinarily no effect after the first day The minor conflicts in various reports are probably due to differences in the methods employed and in the method of interpreting the duration of the insulin effect In this study, insulin effect was considered to be present until hyperglycemia returned to within 10 per cent of the control levels The fact that diet conditions were adjusted in such a manner that sugar levels were maintained at constant values in the patients except when insulin effect was present makes the duration of effect thus demonstrated for single doses convincing It is realized that patients will vary in their individual responses and that the size of the dose determines the timing to some extent However, identical doses of different insulins given to the same patient are undoubtedly comparable, and the effects in the 2 patients were closely comparable For purposes of clinical application, however, no single method can give anything more than relative information concerning various insulins

There are three factors which may be altered in an attempt to vary the time action of globin zinc insulin the globin content the zinc content and the pH This study has shown no significant change in the action of clear acid globin zinc insulin when its globin content was increased from 3.8 to 38 mg per hundred units of insulin with the zinc and the pH kept constant Differences in the curves caused by insulins containing two, five and ten times the globin content of the standard preparation were within the limits of error of the method used The 38 mg globin effect appears to be slightly prolonged However, this insulin was given to only 1 patient, and if the curve obtained is compared with the standard globin insulin curve for that patient (patient A, fig 1), the difference is seen to be negligible It is insignificant when compared with the effect of the excess of protamine in precipitated protamine zinc insulin A clear (acid) protamine zinc insulin has a shorter action than the same modification in precipitated form, as shown by Bailey and Marble⁸ and by unpublished data of Colwell's

When the amount of globin and zinc is reduced to one half of that in the standard preparation, there is a definite alteration in its action This mixture of standard globin zinc insulin and ordinary insulin has an action which is intermediate between the actions of its two component parts It is decidedly more prolonged than that of regular insulin but less so than that of standard globin insulin

Two curves (not included in this report) obtained after administration of preparations in which the zinc content of standard globin

11 Mosenthal, H O Globin Insulin with Zinc in Treatment of Diabetes Mellitus, J A M A 125 483-488 (June 17) 1944

insulin was doubled showed essentially the same timing characteristics as those obtained with standard globin insulin. Thus it would seem that neither increases in the amount of globin nor increases in the zinc content affect the time action of the modified preparation profoundly. Decreasing both of them accelerates and intensifies its activity.

Reiner, Searle and Lang² reported that the duration of insulin effect is decreased and the intensity of action is increased in normal rabbits when the globin or zinc content is lowered.

CLINICAL APPLICATION

Although this investigation was conducted from a purely pharmacologic point of view, certain therapeutic applications of the findings are fairly obvious. They are as follows:

- 1 In therapeutic situations characterized by postprandial glycosuria or nocturnal hypoglycemia or both when protamine zinc insulin is used in large dosage, globin insulin is certainly indicated. Whether or not it will give as good control in such situations as protamine zinc insulin mixtures appears to be a matter which will be decided by the method of trial and error in each individual case. There is no doubt that, in daily morning injections, it will give a more intense daytime insulin effect and wear off more rapidly than protamine zinc insulin but still permit some degree of overlapping from day to day in doses of 60 units or so.

- 2 Acid or clear globin zinc insulin cannot be modified by addition of more globin for the purpose of prolonging its activity or making it less intense. If such modification is desired in any given case, a more appropriate preparation will consist of suitable mixtures of insulin and protamine zinc insulin.

- 3 If increased promptness of action is desired, globin insulin can be supplemented by admixture with ordinary insulin in proportions up to about equal parts. Such mixtures might be useful for occasional patients who tend to show nocturnal hypoglycemia and glycosuria after meals on globin insulin as now manufactured.

- 4 The exact relationship of globin insulin to protamine zinc insulin mixtures cannot be determined from these studies. It appears likely that the standard preparation is approximately similar to the widely used 2:1 mixture (two parts of regular or crystalline insulin thoroughly mixed with one part of protamine zinc insulin). Studies of the exact comparative time action and the predictability of effect of these two insulins with intermediate action are now in process and will be reported soon.

SUMMARY AND CONCLUSIONS

By a method of study based on well stabilized control periods of hyperglycemia and glycosuria in diabetes mellitus of moderate severity,

the following characteristics of 60 unit doses of various globin insulin mixtures in comparison with other insulin preparations were demonstrated

1 Standard globin insulin has a time action which is fairly rapid, showing initial effect within four hours. Its maximum effect is apparent in the concentration of blood sugar in eight to sixteen hours and in that of urine sugar in eight to twenty hours. This effect persists into the second day after the injection is made. Its action is intermediate between that of ordinary insulin in solution and that of protamine zinc insulin.

2 A mixture of equal parts of regular insulin and standard globin insulin has an accelerated and shortened action. It is intermediate between its two components in this respect.

3 Increasing the globin content of standard globin insulin from 3.8 to 38.0 mg per hundred units of insulin does not appreciably alter its time action.

CARDIAC AMYLOIDOSIS

Electrocardiographic and Pathologic Observations

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AND

A STONE FREEDBERG, M D

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CARDIAC amyloidosis is a distinct although rare type of organic heart disease in which the clinical findings are believed to be related to the variable deposition of amyloid in the pericardium, valves, myocardium and smaller blood vessels¹ The purposes of this report are (1) to present 2 cases of cardiac amyloidosis in which electrocardiograms suggested the diagnosis of myocardial infarction, (2) to review the available electrocardiographic data on cardiac amyloidosis and (3) to comment on the relationship of the electrocardiographic findings to the pathologic changes in the myocardium

REPORT OF CASES

CASE 1 —A B, a 67 year old widow, was admitted to the Beth Israel hospital on Aug 30, 1946, because of the swelling of the abdomen of two weeks' duration

Sixteen months before her entry she was seen in the outpatient department because of headache Physical examination at that time revealed a blood pressure of 210 systolic and 115 diastolic millimeters of mercury, the cardiac apex was 3 cm beyond the midclavicular line on percussion, and there was a soft apical systolic murmur There was no evidence of congestive heart failure Ten months before her entry the patient returned because of exertional dyspnea, slight cough and edema of the ankles Blood pressure readings varied between 164 and 145 systolic and 104 and 80 diastolic Urinalysis revealed no albumin or sugar, the white cells numbered 0 to 1 per high power field, and the specific gravity was 1.019 Dyspnea and peripheral edema improved after digitalization

Two weeks before her entry the patient noted the onset of rapidly progressive swelling of the legs and abdomen associated with increasing dyspnea Pain in the chest and paroxysmal dyspnea were absent

This study was aided by a grant from the Life Insurance Medical Research Fund

From the Department of Medicine, Harvard Medical School and the Medical Research Laboratory, Beth Israel Hospital

1 (a) Koletsky, S, and Stecher, R M Primary Systemic Amyloidosis Involvement of Cardiac Valves, Joints and Bones, with Pathologic Fracture of the Femur, Arch Path 27 267 (Feb) 1939 (b) Dillon, J A, and Evans, L R Primary Systemic Amyloidosis, Ann Int Med 17 722, 1942 (c) Lindsay, S The Heart in Primary Systemic Amyloidosis, Am Heart J 32 419, 1946

Examination showed a chronically ill, dyspneic and orthopneic woman with slight icterus and cyanosis. The tongue was red and atrophic. The chest was emphysematous, and fine rales were audible at the right base and the right axilla. The heart was enlarged to the left and the rhythm regular at a rate of 56. There was a soft basal and a louder apical systolic murmur, the blood pressure was 170 systolic and 90 diastolic. The liver filled the upper half of the abdomen, the edge was hard, sharp and nontender and the surface grossly irregular. There were ascites and considerable edema of the abdominal wall, the sacrum and both legs to the thighs.

The specific gravity of the urine ranged from 1.013 to 1.020, the sediment contained 0 to 10 white cells per high power field. Of 6 specimens, 1 contained

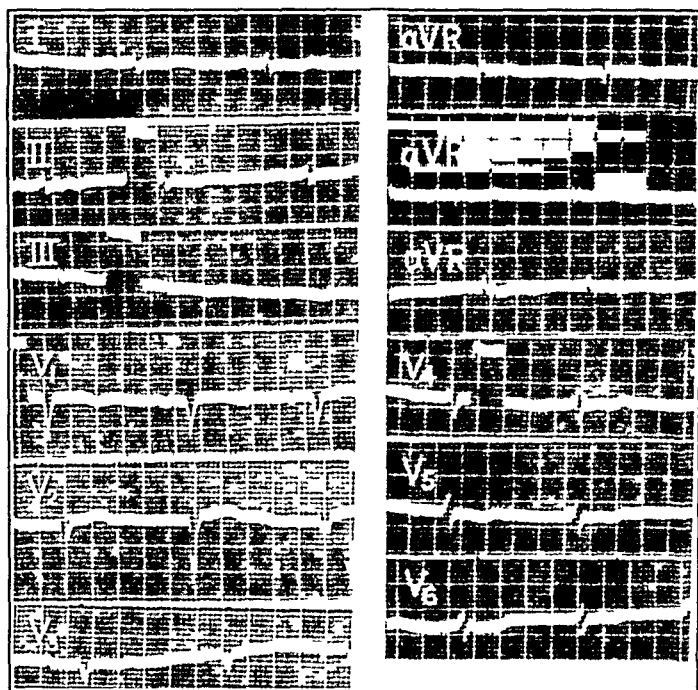


Fig 1—Cardiac amyloidosis. Electrocardiogram of patient A. B. on Sept. 5, 1946. Sinus arrhythmia and bradycardia are present, with a rate of 55 to 70. The P-R interval is 0.20 second and the QRS interval 0.09 second. Low voltage is evident. There are inverted monophasic QRS complexes in leads V_1 and V_2 and a tiny R wave followed by a notched S wave in lead V_3 . T waves are shallow and diphasic in leads I, II, III and V_3 , V_4 , V_5 and V_6 and upright in leads V_1 and V_2 .

albumin (1 plus) and 3 gave a green reaction to the test for sugar. Urobilinogen was present in the urine in dilutions of 1 to 40 on two occasions. The red blood cell count was 4,900,000, with 100 per cent hemoglobin. The leukocytes numbered 6,200, with 56 per cent neutrophils, 41 per cent lymphocytes and 3 per cent monocytes. The reaction of the stool to the guaiac test was 1 plus on two occasions. The reactions to Hinton and Kahn tests of the blood were negative. The fasting blood sugar was 101 mg per one hundred cubic centimeters on one occasion, the icteric index ranged between 16 and 23 units. The serum cholesterol and serum esters were 146 and 101 mg per one hundred cubic centimeters respectively. The total serum protein was 5 Gm per hundred cubic centimeters, with an albumin-globulin ratio of 1. The blood sodium content as sodium chloride was 638 mg

per hundred cubic centimeters The blood nonprotein nitrogen ranged from 31 to 52 mg per hundred cubic centimeters The prothrombin time on the patient's admission to the hospital was 19.4 seconds (normal control, 13.7 seconds), and one week later it was 20.9 seconds (normal control, 14.3 seconds) The "decholin" circulation time and the venous pressure on admission were 19 seconds and 200 mm of water respectively

On roentgenologic examination the heart was enlarged to the left and right and the lungs were congested

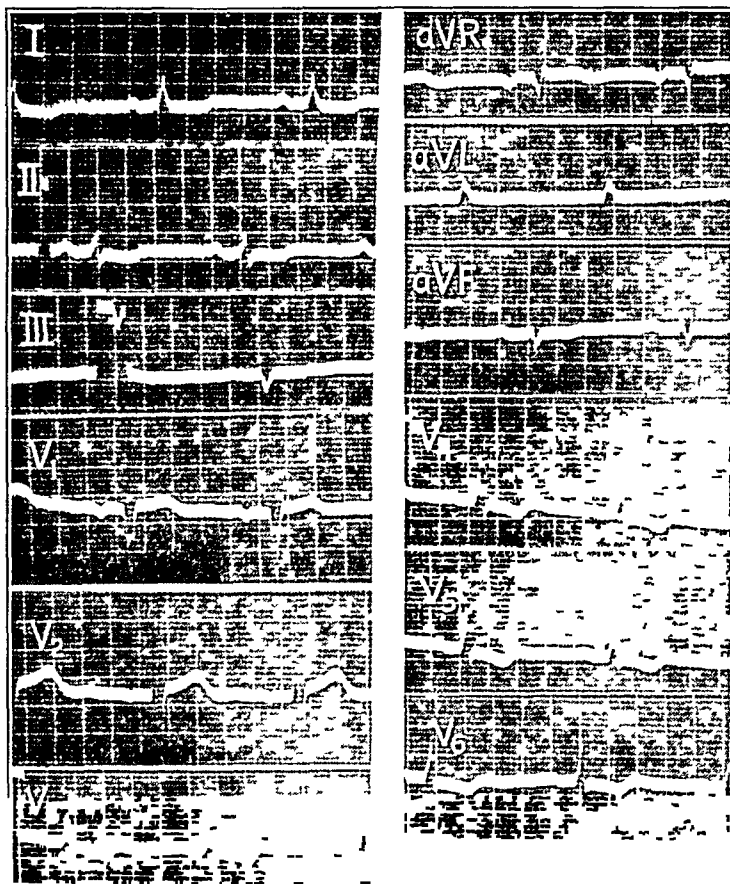


Fig 2—Cardiac amyloidosis. Electrocardiogram of patient A. B. on Sept 10, 1946. Sinus bradycardia is present, with a rate of 58. There is left axis deviation. The P-R interval is 0.24 second and the QRS interval 0.10 second. There is an inverted monophasic QRS complex in lead V_1 , a tiny R wave in lead V_2 and a diphasic T wave in leads I, II, aVL and aVF . There is an inverted T wave in leads V_3 , V_4 , V_5 and V_6 . Low voltage is evident.

A twelve lead electrocardiogram on the sixth day in the hospital (fig 1) showed abnormalities, particularly of the Q waves in leads V_1 and V_2 and the low R wave in lead V_3 , which were interpreted as indicative of probable old anterior myocardial infarction. A second electrocardiogram (fig 2) on the eleventh day showed changes characterized by a prolonged P-R interval, taller R waves in leads V_3 , V_4 , V_5 and V_6 and T wave inversion.

The patient was afebrile throughout her stay in the hospital. The blood pressure readings varied from 140 to 110 systolic and from 70 to 60 diastolic millimeters of mercury. Although the patient received adequate amounts of digitalis and mercurial diuretics, she grew progressively weaker and apathetic and eventually became disoriented and incontinent. She died on the twenty-ninth day in the hospital.

*Autopsy Observations**—The principal finding at autopsy was generalized primary amyloidosis. This was most pronounced in the heart, liver, spleen and adrenals and less pronounced in the lungs, pancreas, kidney and uterus.

Other observations at autopsy included arteriosclerosis of the aorta, early basal lobular pneumonia, dependent edema, ascites, icterus, congestion of the gastro-

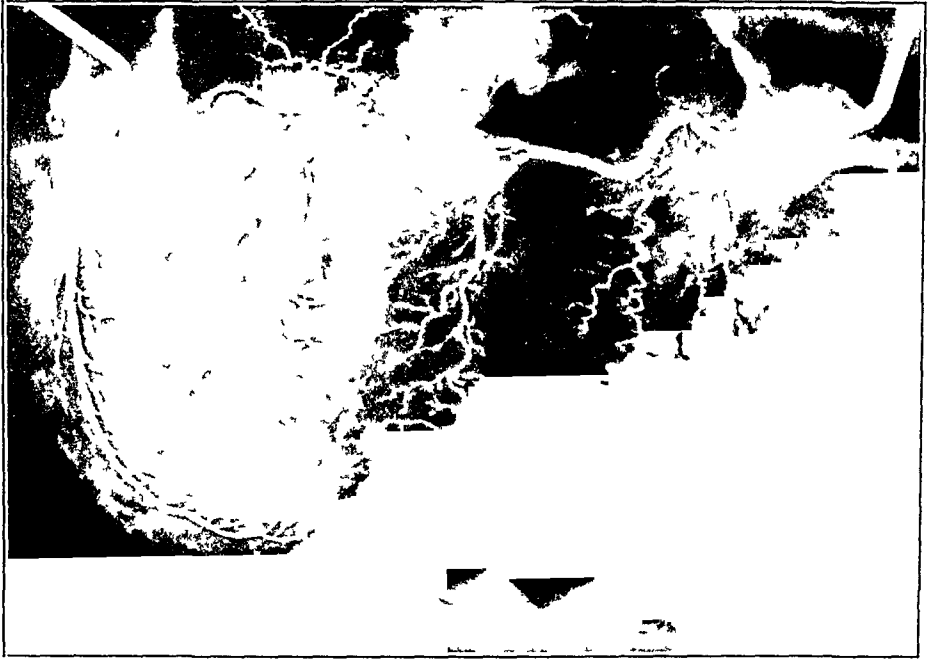


Fig 3—Roentgenogram of the unrolled heart (Schlesinger method) showing normal coronary arteries. No calcification, narrowing, occlusion or interarterial anastomoses are demonstrated.

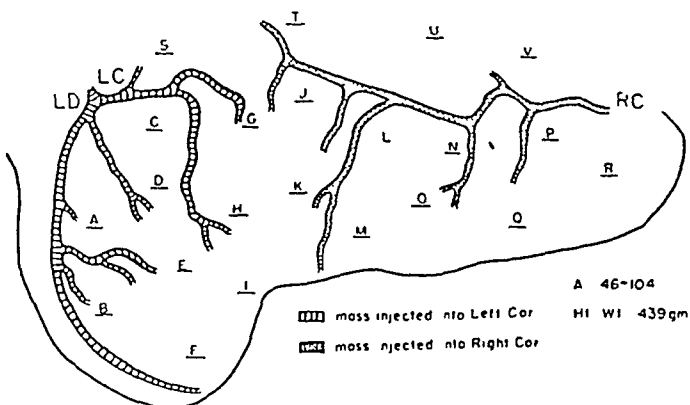


Fig 4—Diagram of injected heart showing location of microscopic sections. LD indicates left descending coronary artery, LC left circumflex coronary artery, RC right coronary artery and A-V labeled multiple sections taken for microscopic study.

2 Dr. Monroe J. Schlesinger offered guidance in the preparation of the pathologic material.

intestinal tract, bile stasis, early cirrhosis of the liver, cholesterosis of the gall-bladder, hyaline arteriolopathy of the spleen, multiple calcified involutonal nodules of the thyroid, fibroma of the kidneys, multiple leiomyomas of the uterus, focal adenomyosis and cystic atrophy of the endometrium

The heart weighed 439 Gm. It was free from softening, fibrosis, abscess or tumor, the myocardium was red-brown and waxy. The pericardium, the epicardial and endocardial surfaces of the heart and the valves revealed no pathologic changes.

The coronary arteries, injected, examined roentgenologically and dissected after the method of Schlesinger,³ revealed no evidence of calcification, narrowing, occlusion or anastomoses in the visualized coronary tree (fig. 3)



Fig 5—Representative area of myocardium showing diffuse and extensive deposition of amyloid between the sarcolemma of muscle fibers and the endothelium of interstitial capillaries. Dark-staining areas represent atrophic muscle fibers. Hematoxylin and eosin stain, $\times 90$, wratten B filter.

Numerous multiple sections were taken from representative portions of the heart, as indicated in figure 4. Microscopically these sections revealed diffuse and extensive deposition of amyloid between the sarcolemma of the muscle fibers and the endothelium of the interstitial capillaries. The myocardial fibers were atrophic, and every section revealed areas, in some instances amounting to two or three adjacent low power fields, where muscle was almost completely replaced by coalescent masses of amyloid (fig. 5). There was no fibrosis or inflammatory reaction.

³ Schlesinger, M. J. An Injection Plus Dissection Study of the Coronary Arteries, *Am Heart J* 15:528, 1938.

All sections contained amyloid in the walls of blood vessels. This was noted in capillaries, venules, and arterioles and to a lesser extent in the veins and arteries. A conspicuous and frequent finding was the extreme narrowing and complete occlusion of many of the arterioles and smaller arteries by the subendothelial accumulation of amyloid (fig 6). The internal diameters of the lumens of occluded vessels were found to range up to 0.2 mm and those of narrowed vessels to 0.4 mm. Although amyloid was found in vessel walls with lumen diameters greater than 0.4 mm, there was no narrowing in these vessels.

No appreciable differences were observed in either the amount of amyloid deposited or the amount of muscle replaced from section to section. There were, in addition, no differences in amyloid deposition or muscle replacement between the endocardial and epicardial portions of each section.

Comment—Careful study of the heart demonstrated the absence not only of myocardial infarction or fibrosis but also of any arteriosclerotic disease of the coronary arteries. It is, therefore, believed that the electrocardiographic picture, which suggested infarction, can be ascribed to the effect of amyloid on the myocardium.

CASE 2—D L, a 50 year old meat cutter, was admitted to the Beth Israel Hospital on Sept 30, 1946, because of swelling of the abdomen of two months' duration. He had been entirely well until two years before his entry, when he noticed the onset of fatigue. Nine months before entry he noted increasing fatigability, associated with weakness, anorexia, slight but progressive exertional dyspnea and edema of the ankles in the evening. He was seen by his physician two months before entry because of pain in the shoulder, paroxysmal nocturnal dyspnea and "enlargement of the stomach" associated with epigastric distress following meals. He was told that he had a large liver and was advised to enter the hospital for further study. There had been a loss of weight of 7 pounds (3.2 Kg) in the past six months. There had been no history of pain in the chest.

Physical examination showed a pale middle-aged man in no acute distress. There was slight elevation of the right side of the diaphragm and dulness and diminished breath sounds at the base of the right lung, rales were heard at the base of both lungs. The heart did not appear enlarged, the apex impulse being within the midclavicular line. There were occasional extrasystoles, and a diastolic gallop rhythm was heard over the precordium. The pulmonic second sound was louder than the aortic second sound. There was a short blowing grade I systolic murmur at the apex. The blood pressure was 140 systolic and 64 diastolic. The liver was markedly enlarged and slightly tender, and the right lobe was irregular though no nodules were palpated. The spleen was felt 3 cm below the left costal margin. There was no peripheral edema.

The urine showed concentrating power to 1024. Seventeen specimens were normal except for occasional white cells, a 1 plus and a 2 plus reaction for albumin in 2 specimens and a green reaction for sugar in 4. Determinations of urobilinogen in 8 specimens showed positive reactions in dilutions ranging from 1:10 to 1:80.

The red blood cell count was 4,500,000, with 90 per cent (13.0 Gm) hemoglobin. The leukocytes numbered 9,400 with 65 per cent neutrophils, 30 per cent lymphocytes and 5 per cent monocytes. The stool did not contain mucus or blood on three examinations. Reactions to Hinton and Kahn tests of the blood were negative.

The fasting blood sugar was 119 mg per hundred cubic centimeters. The icteric index was 13 units. The serum cholesterol and serum cholesterol esters were 202 and 99 mg per hundred cubic centimeters respectively. The total serum protein was 6.5 Gm per hundred cubic centimeters, with an albumin-

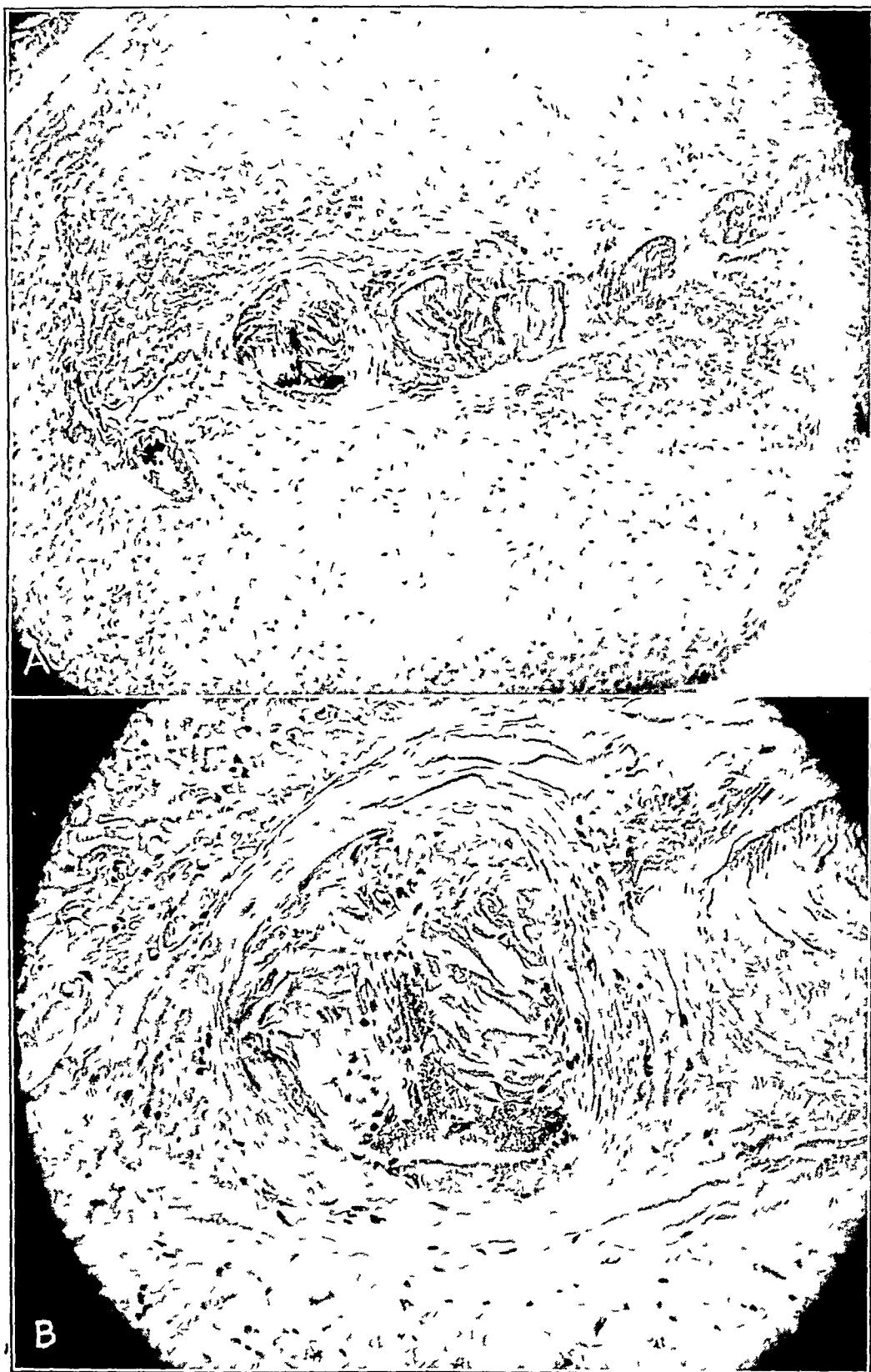


Fig 6—*A*, example of extreme arteriolar narrowing produced by subendothelial accumulation of amyloid. Dark-staining material in vessel lumen is injected radiopaque mass. Congo red stain, $\times 78$, wratten G filter. *B*, higher magnification of vessel shown in *A* demonstrating endothelial lining separating injection mass in lumen from subendothelial amyloid. Congo red stain, $\times 250$, wratten G filter.

globulin ratio of 16 The prothrombin time was 186 seconds (normal control, 140 seconds) The "decholin" circulation time and the venous pressure were 16 seconds and 150 mm of water respectively The erythrocyte sedimentation rates were 0.45 and 0.1 mm per minute (normal, 0.08 to 0.35 mm per minute)⁴ The sulfobromophthalein test showed 95 per cent retention of the dye in five minutes and 35 per cent retention in half an hour The basal metabolic rate was -12 per

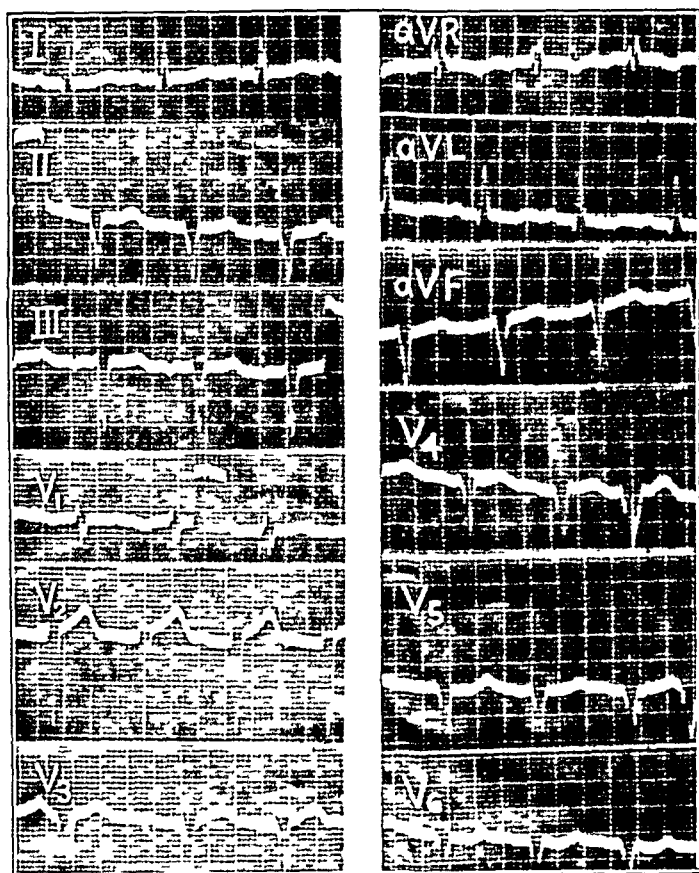


Fig 7—Cardiac amyloidosis Electrocardiogram of patient D. L. on Oct. 1, 1946 There are ventricular premature beats, a rate of 85 and left axis deviation The P-R interval is 0.22 second and the QRS interval 0.11 second There is a small Q wave in leads I and aVL and prominent Q waves in leads V₃, V₄, V₅ and V₆ The QRS complexes are notched, and there is a prominent R wave in lead aVR

cent In a congo red test there was 45 per cent retention of the dye in one hour The cephalin flocculation and galactose tolerance tests both elicited negative reactions A biopsy of the liver performed on the twentieth day in the hospital revealed amyloidosis Roentgenologically the transverse cardiac diameter was 16.0 cm and the transverse thoracic diameter 29.5 cm

A twelve lead electrocardiogram on the second day in the hospital (fig. 7) and another tracing on the nineteenth day (fig. 8) showed first degree heart block, probable incomplete bundle branch block on the right, and Q waves in leads I, aVL and V₃, V₄, V₅ and V₆ suggestive of old anterior myocardial infarction A

⁴ Rourke, D. M., and Ernstene, A. C. A Method for Correcting the Erythrocyte Sedimentation Rate for Variations in the Cell Volume Percentage of the Blood, *J. Clin. Investigation* 8: 545, 1930

third tracing on the forty-second day (fig 9) showed irregularities in the rhythm and rate in addition to an inverted monophasic QRS complex in lead V_3 .

During a period in the hospital of sixty-eight days the patient experienced one brief episode of pressing substernal pain, relieved by nitroglycerine. Digitalis, diuretics and a variety of dietary supplements had no effect on the clinical course. Five weeks after discharge the patient was hospitalized at the Veterans Administration Hospital, West Roxbury, Mass., where he died suddenly on March 21, 1947. Permission for autopsy was not obtained.

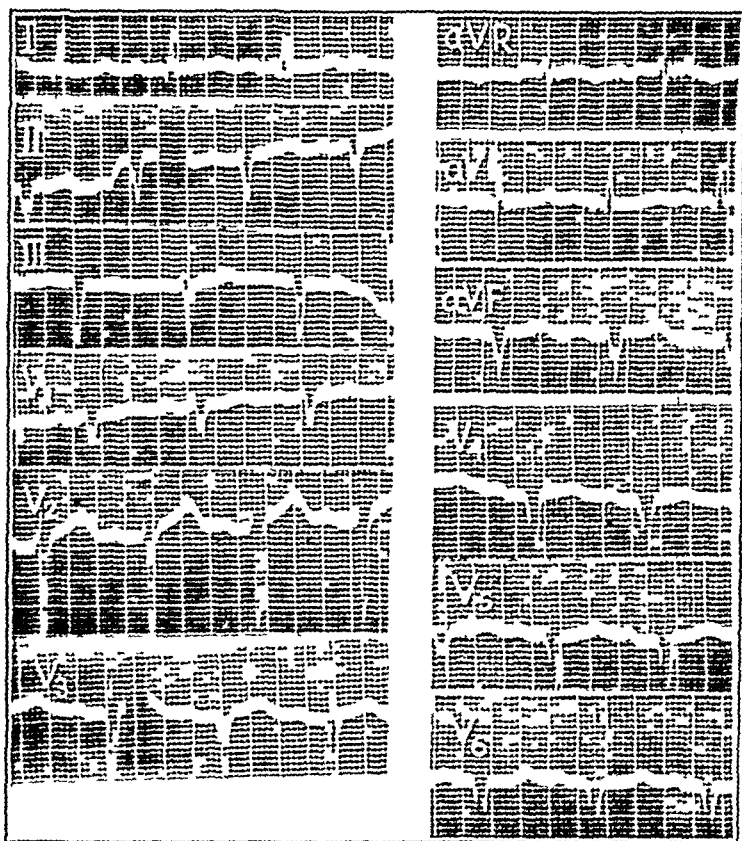


Fig 8—Cardiac amyloidosis. Electrocardiogram of patient D. L. on Oct 19, 1946. There is normal sinus rhythm, with a rate of 75. Left axis deviation is present. The P-R interval is 0.23 second and the QRS interval 0.11 second. There is a small Q wave in leads I and aVL, and there are prominent Q waves in leads V_3 , V_4 , V_5 and V_6 . A small R wave in lead V_1 is followed by a notched wide S wave.

Comment—In this case the diagnosis of amyloidosis was established by biopsy of the liver. Although confirmation at autopsy is lacking, it is believed that the abnormal electrocardiograms recorded represented extensive involvement of the myocardium by amyloid rather than by infarction.

COMMENT

A review of the literature⁵ and of the case records of four Boston hospitals⁶ has revealed 64 cases of cardiac amyloidosis of unknown

5 (a) Kalbfleisch, H. H. Amyloidosis of Heart, Frankfurt Ztschr. f. Path. 54:319, 1940. (b) Rodriguez, M., and Valente, P. Atypical Generalized Amyloidosis, Rev. clin. españ. 10:310, 1943. (c) Sisalo, P., and Ritama, V.

(Footnotes continued on next page)

origin,⁷ 11 previously unreported. In all cases with the exception of case 2 herein presented the heart was studied after death. Electrocardiograms were recorded in 19 of the 53 published cases but reproduced in only 6 instances, whereas they were recorded and available in 6 of the unreported cases, including the 2 presented in this paper. Three cases in which electrocardiograms were recorded were excluded from

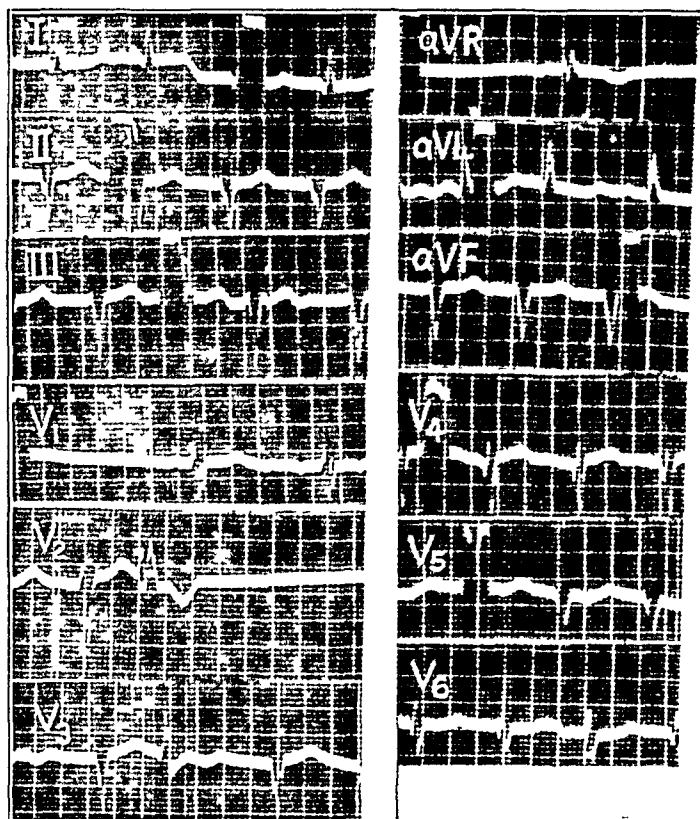


Fig 9—Cardiac amyloidosis. Electrocardiogram of patient D L on Nov 12 1946. Sinus arrhythmia, ventricular extrasystoles from different foci, marked sinus bradycardia in lead aVR (rate, 26), long sinus pause and left axis deviation are present. A small Q wave in leads I and aVL, an inverted monophasic QRS complex in lead V₃, a prominent Q wave in leads V₄, V₅ and V₆ and an early R wave followed by a wide-notched S wave in leads V₄, V₅ and V₆ can be seen.

Atypical Amyloidosis with Special Consideration of Heart, *Acta med Scandinav* **116** 260, 1944 (d) Wells, A H, and Goldish, D R. Diagnostic Case Report (Clinical Pathologic Conference), *Minnesota Med* **28** 920, 1945 (e) Eisen, H N. Primary Systemic Amyloidosis, *Am J Med* **1** 144, 1946 (f) Ranstrom, S. Amyloidosis Myocardii, *Acta med Scandinav* **123** 111, 1946 (g) Orloff, J, and Felder, L. Primary Systemic Amyloidosis. Jaundice as Rare Accompaniment, *Am J M Sc* **212** 275, 1946 (h) Diffuse Plasma-Cell Myeloma. Lower Nephron Nephrosis (Bence-Jones Proteinuria Type), Atypical or "Primary" Amyloid Disease, Involving Muscles, Joints, Heart and Blood Vessels, *Cabot Case* 32231, *New England J Med* **234** 763, 1946. Lindsay¹⁰

6 In addition to the case reports of the Beth Israel Hospital, records were reviewed at the Boston City Hospital through the courtesy of Dr Lawrence Ellis,

further study because they were complicated by the coexistence of significant arteriosclerotic coronary artery disease

The electrocardiographic findings in the remaining 22 cases⁸ are summarized in the accompanying table. It is apparent that although there was no uniform pattern some variation from the normal was recorded in all instances. Moreover, in 4 cases in which more than one electrocardiogram was obtained changes were observed from one tracing to the next. These consisted of variations in the T waves⁹ and in the P-R interval, QRS duration and Q waves^{8g}

Analysis of Electrocardiograms in 22 Cases of Cardiac Amyloidosis

Age	36 to 80 years—Average, 57 years
Sex	11 Men, 11 Women
Congestive heart failure	17
Angina pectoris	4
Hypertension	3
Heart weight	240 to 750 Gm—Average, 463 Gm
Cases in which 3 or 4 leads were obtained	19
Cases in which multiple CF leads were obtained	1
Cases in which unipolar leads were obtained	2
	<i>No of Cases</i>
Prolonged P-R interval	6
Low voltage	12
Bundle branch block (standard leads only in 2)	3
Deep Q waves (in unipolar precordial leads)	2
ST and T wave abnormalities	12
Axis deviation	9

In the 2 cases reported here, in which unipolar limb and precordial leads were obtained, the electrocardiograms were suggestive of myocardial infarction. In case 1 cardiac pain was absent and gross and microscopic study of the heart did not reveal myocardial infarction or fibrosis. This case supports the view of Wilson,¹⁰ who recently stated

at the Massachusetts General Hospital through the courtesy of Dr J H Means and at the Peter Bent Brigham Hospital through the courtesy of Dr George Thorn

7 Although cardiac involvement has been noted in the so-called secondary type of amyloidosis, it is not as frequent or as extensive as in the atypical or so-called primary form of the disease. This report deals only with cardiac amyloidosis of the latter type

8 (a) Kerwin, A J Idiopathic Amyloid Disease of the Heart, *J Lab & Clin Med* **22** 255, 1936 (b) De Navasquez, S, and Treble, H A A Case of Primary Generalized Amyloid Disease with Involvement of Nerves, Brain **61** 116, 1938 (c) Haenisch, R Ein Fall von Paramyloidose, Frankfurt *Ztschr f Path* **52** 107, 1938 (d) Binford, C A Primary Amyloid Disease of Myocardium and Blood Vessels Report of Case with Death from Myocardial Failure, *Arch Path* **29** 314 (March) 1940 (e) Pearson, B, Rice, M M, and Dickens, K L Primary Systemic Amyloidosis Report of Two Cases in Negroes, with Special Reference to Certain Histologic Criteria for Diagnosis, *ibid* **32:1** (July) 1941 (f) Sappington, S W, Davie, J H, and Horneff, J A Primary Amyloidosis of the Lungs, *J Lab & Clin Med* **27** 882, 1942, (g) Six previously unreported cases of primary amyloidosis, with electrocardiograms Footnotes 1b and c and 5a, b, c, d, e and f

9 DeNavasquez and Treble^{8b} Footnote 8g

10 Wilson, F N, Johnston, F D, Rosenbaum, F F, and Barker, P S On Einthoven's Triangle, the Theory of Unipolar Electrocardiographic Leads, and the Interpretation of the Precordial Electrocardiogram, *Am Heart J* **32**:309, 1946

that "it is imperative to avoid making a clinical diagnosis [of myocardial infarction] on the basis of electrocardiographic examination, when after adequate investigation, it is certain that this diagnosis is not supported by the history and other clinical data" The unipolar leads, although of no aid in establishing an etiologic or pathologic diagnosis, did indicate better than the standard leads alone the extent, but not the location, of the cardiac changes found at the postmortem examination

The mechanism by which these electrocardiographic abnormalities are produced is not apparent At least three factors, alone or in combination, may be responsible for the findings They are (1) the narrowing and obliteration of the small arteries, (2) the loss of muscle and (3) the electrical properties of amyloid itself

The extensive replacement and atrophy of muscle may have been produced either directly by the pressure of pericapillary and hence perimuscular amyloid or secondarily by ischemia from obliterated small arterial channels If the latter mechanism were prominent in the production of the pathologic picture, one might expect to see an increase in the normal fibrous stroma or a condensation of it That such an increase was not found lends support to the view that the muscle replacement resulted primarily from the perimuscular accumulation of amyloid In such an apparently slow process, however, it is not possible to decide by histopathologic evidence to which mechanism the diminution of muscle mass was due

The large amount of amyloid present in the various sections suggests the possibility that this substance may affect the propagation of an electrical impulse through the heart The physicochemical properties of amyloid and its position in relation to the cell membrane, as well as the properties of the cell membrane itself, are not sufficiently understood to permit more than a mention of the possible role of this substance in the production of the observed electrocardiographic abnormalities

SUMMARY AND CONCLUSION

1 Cardiac amyloidosis is associated with a wide variety of changing electrocardiographic phenomena including prolonged P-R and QRS intervals, low voltage, deep Q waves and variations in T waves

2 The electrocardiogram in cases of cardiac amyloidosis may be indistinguishable from that observed in cases of myocardial infarction Two cases of the latter have been presented, in 1 of which the absence of myocardial infarction or fibrosis was conclusively demonstrated by careful pathologic study of the heart

3 Although the mechanism by which "electrocardiographic infarction" is produced in cardiac amyloidosis is not apparent, the existence of such patterns emphasizes the need for caution in making a diagnosis of myocardial infarction from the electrocardiogram alone

MYENTERIC PLEXUS IN CONGENITAL MEGACOLON

Study of Eleven Cases

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AND

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SINCE 1886, when Hirschsprung¹ published a report entitled "Sluggishness of the Stool in the Newborn, Resulting from Dilatation and Hypertrophy of the Colon," there have been many reports in the medical literature describing various aspects of megacolon. Generally, the name "Hirschsprung's disease" has been applied to the cases of megacolon reported in the literature but, as Finney² has pointed out, there were many reports of cases of megacolon in the literature antedating those of Hirschsprung. For this reason, in our opinion the descriptive term "megacolon" rather than the less precise eponym should be applied to these cases.

Cases of megacolon are rarely encountered.³ Perhaps as a result of the rarity of the condition, there have been few descriptions of the gross pathologic characteristics of megacolon. There have been a few reports⁴ of single cases of megacolon in which the myenteric plexus was studied by microscopic pathologic methods. Except for the studies of Etzel⁵ on megaesophagus and megacolon of the acquired type, there has been no series of cases reported in which the micropathologic characteristics of megacolon were studied.

Abridgment of thesis submitted by Dr. Whitehouse to the Faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of M. S. in Medicine.

Dr. Kernohan is from the Section on Pathologic Anatomy, Mayo Clinic.

1 Hirschsprung, Stuhltragheit Neugeborener in Folge von Dilatation und Hypertrophie des Colons, *Jahrb. f. Kinderh.* **27** 1-7, 1886.

2 Finney, J. M. T. Congenital Idiopathic Dilatation of the Colon, *Surg., Gynec. & Obst.* **6** 624-643 (June) 1908.

3 (a) Whitehouse, F., Bergen, J. A., and Dixon, C. F. Congenital Megacolon. Favorable End Results of Treatment by Resection, *Gastroenterology* **1** 922-937 (Oct.) 1943. (b) de Takats, G., and Biggs, A. D. Observations on Congenital Megacolon, *J. Pediat.* **13** 819-846 (Dec.) 1938. (c) Biggs, A. D., and de Takats, G. Congenital Megacolon, *Am. J. Dis. Child.* **55** 1348-1351 (June) 1938.

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The facts known in the past concerning the etiologic factors and pathogenesis of congenital megacolon have not been based on studies of the micropathologic characteristics of the colon. In the past forty years there have been several hypotheses concerning the etiologic factors and the pathogenesis of congenital megacolon, all of which were similar in their basic principle. Hawkins⁶ in 1907, in a discussion of megacolon, stated that "if by congenital inertness of the colon we mean a neuromuscular defect, through which a section of the colon, though it opposes no obstacle is yet (continuously or from time to time) incapable of forwarding its contents, I believe we have in this the basis of the disease." Alvarez⁷ stated that the simplest explanation for the production of megacolon would be a loss of function in certain ganglion cells in the intestinal plexuses. Hurst⁸ stated that he thought megacolon was due to a disturbed innervation of the colon which took the form of an underactivity of the parasympathetic autonomic fibers to the anal sphincter.

4 (a) Tittel, K. Ueber eine angeborene Missbildung des Dickdarmes, *Wien klin Wchnschr* 14 903-907, 1901. (b) Tiffin, M. E., Chandler, L. R., and Faber, H. K. Localized Absence of the Ganglion Cells of the Myenteric Plexus in Congenital Megacolon, *Am J Dis Child* 59 1071-1082 (May) 1940. (c) Brentano. Ueber einen Fall von Hirschsprung'scher Krankheit, *Verhandl d deutsch Gesellsch f Chir* 33 265-268, 1904. (d) Dalla Valle, A. Ricerche istologiche su di un caso di megacolon congenito, *Pediatria* 28 740-752, 1920. (e) Familial Megacolon, *ibid* 32 569-599 (May 15) 1924. (f) Cameron, J. A. M. On Aetiology of Hirschsprung's Disease, *Arch Dis Childhood* 3 210-211 (Aug) 1928. (g) Amorim, M., and Correa Netto, A. Histopathologia e pathogenese do megasophago e megarecto (Considerações em torno de um caso de "mal de engasgo"), *Am Fac de med de São Paulo* 8 101-127, 1932. (h) Perrot, A., and Danon, L. Obstruction intestinale de cause rare, chez un nourrisson, *Ann d'anat path* 12 157-165 (Feb) 1935. (i) Robertson, H. E., and Kernohan, J. W. Myenteric Plexus in Congenital Megacolon, *Proc Staff Meet, Mayo Clin* 13 123-125 (Feb 23) 1938.

5 Etzel, E. (a) Megaoesophagus and Its Neuropathology. Clinical and Anatomic-Pathological Research, *Guy's Hosp Rep* 87 158-174 (April) 1937. (b) La dilatacion del esofago frente a las lesiones del plexo de Auerbach en el megasofago, *Bol y trab de la Soc de cir de Buenos Aires* 21 131-148 (May 5) 1937. (c) O megacolon e seu conceito moderno, *Arch argent de enferm d ap digest y de la nutricion* 17 123-184 (Dec-Jan) 1941-1942. (d) Distribuição geografica a do megasofago-megacolon estado atual da teoria etiologica da avitaminose B₁, estudo de 626 casos, *Rev Assoc paulista de med* 15 103-158 (Aug) 1939. (e) Neuropatologia do megasofago e megacolo estudo de 5 casos, *Ann Fac de med de São Paulo* 10 383-395, 1934. (f) O megacolon como symptoma de uma doença systematisada, *Brasil-med* 53 823-827 (Aug 19) 1939.

6 Hawkins, H. P. Remarks on Idiopathic Dilatation of the Colon, *Brit M J* 1 477-483 (March 2) 1907.

7 Alvarez, W. C. An Introduction to Gastro-Enterology, ed 3, New York, Paul B. Hoeber, Inc., 1940, pp 218 and 283.

8 Hurst, A. F. Anal Achalasia and Megacolon (Hirschsprung's Disease Idiopathic Dilatation of the Colon), *Guy's Hosp Rep* 84 317-350 (July) 1934.

Bockus⁹ recently stated that "the literature on megacolon contains no records to support the *frequent* [our italics] occurrence of degenerative or inflammatory changes in the nerve cells of Auerbach's plexus around the anal sphincters. If such changes were found, strong evidence in favor of anal achalasia would be at hand."

Certain experimental observations on the production of megacolon in animals have seemed to support the foregoing hypotheses. Ishikawa¹⁰ stated that in his opinion congenital megacolon is due to a congenital disturbance of the sacral autonomic nerves. He sectioned the sacral autonomic inflow (parasympathetic) to the colon in 12 dogs and found that in 9 constipation developed as the result of this procedure, in 8 dilatation of the colon developed, 7 had hypertrophy of the colon and 4 showed degeneration of the "intramural nerve fibers." He also reported 3 cases of acquired megacolon in which he demonstrated scars of the mesosigmoid involving the sacral autonomic nerves. He considered this to be the cause of the megacolon in the 3 cases. He also sectioned both parasympathetic and sympathetic nerves to the colon in 2 dogs and demonstrated the same results as those obtained by parasympathetic section alone. Adamson and Aird¹¹ produced megacolon in cats by the section of the sacral autonomic fibers. Kleinschmidt¹² obtained experimental results similar to those of Ishikawa and Adamson and Aird.

On the basis of the foregoing theoretic and experimental observations, it has been our feeling that one approach to the study of the origin and pathogenesis of congenital megacolon would be the study of the myenteric plexus (plexus of Auerbach) of the colon in cases of congenital megacolon in which postmortem examination had been performed. The myenteric plexus apparently has as its main function in the colon the conduction of stimuli and the coordination of movements¹³ and, as a result of such function, would be of importance in any consideration of the pathogenesis of congenital megacolon.

PREVIOUS STUDIES OF THE MYENTERIC PLEXUS IN CASES OF MEGACOLON

In 1901 Tittel,^{4a} in a report of 1 case, noted that the ganglion cells of the myenteric plexus at various levels of the large intestine were

9 Bockus, H. L. *Gastro-Enterology*, Philadelphia, W. B. Saunders Company, 1943, vol. 2, p. 404.

10 Ishikawa, N. *Experimentelle Untersuchungen über die Dickdarminnervation, insbesondere des Colon descendens et sigmoideum*, *Mitt. a. d. med. Fak. d. k. Univ. Kyushu Fukuoka* 7:295-338, 1923, *Experimentelle und klinische Untersuchungen über die Pathogenese und das Wesen des Megakolons*, *ibid.* 7:339-400, 1923.

11 Adamson, W. A. D., and Aird, I. *Megacolon: Evidence in Favour of a Neurogenic Origin*, *Brit. J. Surg.* 20:220-233 (Oct.) 1932.

12 Kleinschmidt, cited by Bockus.⁹

13 Alvarez,⁷ p. 46.

scanty and showed degenerative changes. He concluded that the normal course of peristalsis might have been influenced unfavorably by the abnormal state of the myenteric plexus.

In 1904 Brentano,^{1c} in a report of 1 case, stated that the nerve elements in the large intestine were weakly developed but failed to state from what part the sections were taken.

In 1920 Dalla Valle^{4d} reported a case of congenital megacolon, with death of the patient at the age of 10½ months. In 1924 he^{4e} reported the occurrence of megacolon in the child's brother. In both cases many sections of various portions of the large intestine were carefully examined, with special reference to the nerve cells of the myenteric plexus. This was the first time that a really comprehensive study of the myenteric plexus had been made. In the first case the ascending, transverse and descending portions of the colon were greatly enlarged but the sigmoid flexure was of normal caliber. In the ascending colon the cells of the myenteric plexus were few and small, in the transverse and descending colon they were normal in appearance while in the sigmoid colon they were absent. In the second case the extent of colonic enlargement was almost exactly the same, the transition from the descending colon to the sigmoid colon was sharply marked, and within a linear distance of 3 cm the intestinal caliber returned to normal. The cells of the myenteric plexus were normal in number in the appendix, cecum and ascending, transverse and descending colon, but in more than 100 sections from the sigmoid colon no nerve cells could be found.

In 1927 and 1928 Cameron¹⁴ reported studies on 2 cases of megacolon apparently congenital in type. He found no change in the myenteric plexus of the distended and hypertrophied colon except for some fibrous change. The colonic distention stopped at the pelvic rectal sphincter, and sections taken in this region showed that "in the intermuscular plexus of nerve cells the changes are of striking character, the ganglia are replaced by inflammatory cells." Cameron felt that these changes were in the nature of a destructive lesion of the nerve ganglia at the pelvic rectal sphincter.

In 1932 Amorim and Correa Netto^{4g} reported a case of megaesophagus and megacolon (of the acquired type). In this case there were microscopic changes in the plexus of Auerbach of the colon and esophagus.

In 1934 Etzel^{5b} reported briefly on studies of the myenteric plexus in 4 cases of megacolon which concomitantly was associated with megaesophagus. He stated that he considered these to be cases of acquired

14 Cameron, J. A. M. Oesophagectasia in Child, *Arch. Dis. Childhood* 2: 358-360 (Dec.) 1927, footnote 4 f.

megacolon and megaesophagus and not cases in which the dilatation was congenital in origin. He stated that the myenteric plexus in the lower part of the terminal intestine always presented lesions, which were described as a disappearance of the nerve cells, and cicatrices of the ganglions of the myenteric plexus of the colon.

In 1935 Perrot and Danon^{4b} reported a case in which an infant died at the age of 15 days as a result of intestinal obstruction. The small intestine was dilated and thickened above a constriction in the lower part of the ileum. The myenteric plexus became abnormal at the point of the constriction, with nerve cells becoming rare from there to the splenic flexure. The authors felt that the hypoplasia of the plexus had caused a functional obstruction.

In 1938 Robertson and Kernohan⁴¹ were the first in North America to describe changes in the myenteric plexus in a case of congenital megacolon. They stated that the ganglion cells and fibers of the myenteric plexus were definitely smaller than normal and were vacuolated and that the ganglion cells were either absent or imperfectly formed. They also mentioned that the same appearance was noted in several other cases of megacolon.

In 1937 Etzel^{5a} reported further studies on the myenteric plexus in 8 cases of acquired megacolon. The changes noted were similar to those described in the plexus of the esophagus, which were dislocation of the nucleus to the periphery, central chromatolysis, microvacuolation, macrovacuolation and degeneration of the protoplasm. Pyknosis of the nucleus, expulsion of the nucleus, destruction of the neurofibrillar system and neuronophagia were also described. The dendrites were observed to swell, and their extremities became globular. The alterations of the axis-cylinder were classified as cleavage, retraction balls of Cajal, "effilochement" of Cajal, argentophilia and thickening and fragmentation.

In 1940 Tiffin, Chandler and Faber^{4b} reported a careful study of a case of congenital megacolon in which the patient was a child 20 months of age. There was roentgenographic evidence of progressive dilatation of the entire large intestine above the sigmoid flexure without obstructive stenosis, absence of effect from a parasympathetic depressant (syntropan), production of powerful intestinal contractions without propulsion of contents by parasympathetic augmenter drugs (neostigmine and acetyl- β -methylcholine chloride) and by sympathetic depression (spinal anesthesia) and failure of sympathectomy on the left and right lumbar regions to relieve the condition. Tiffin and his associates stated that "sections, along a taenia coli, of the terminal portion of the dilated colon and the grossly normal portion of the sigmoid colon showed a few scattered ganglion cells of Auerbach's myenteric plexus lying between the circular and the longitudinal muscle only in the undilated sigmoid

colon but none in the 7 cm above this region" Unusually abundant nerve fibrils were noted in this region A section taken from the dilated transverse colon showed many ganglion cells Tiffin and his associates felt that the evidence strongly suggested that at least in some cases of megacolon the primary disturbance is a localized interference with the passage of normal peristaltic waves across a given segment of the alimentary tract due to defective innervation This interference, they stated, might consist of an inability of the musculature either to relax (achalasia) or to contract, either of which disturbances would prevent the sequence of alternate relaxation and contraction composing the peristaltic wave and thus would render propulsion of intestinal contents across the involved segment noneffective

TABLE 1—*Collected Series, Reporting Study of Plexus of Auerbach in Cases of Megacolon*

Author and Date	Cases	Changes Reported
Tittel (1901) ^{4a}	1	Scanty ganglion cells in whole colon
Brentano (1904) ^{4c}	1	Nerve elements of the colon weakly developed
Dalla Val'e (1920 and 1924) ^{4d e}	2	No nerve cells in sigmoid Normal nerve cells in rest of colon
Cameron (1927 and 1928) ^{4f}	2	Ganglions near pelvicrectal sphincter replaced by inflammatory cells
Amorim and Correa Netto (1932) ^{4g}	1	Degenerative changes in plexus
Etzel (1937) ^{4b}	8	Absence of plexus in distal end of colon
Perrot and Danon (1935) ^{4h}	1	Hypoplasia of plexus
Robertson and Kernohan (1938) ⁴ⁱ	1	Absence of ganglion cells and other changes in nerve cells
Tiffin and associates (1940) ^{4b}	1	Absence of ganglion cells in sigmoid
Total	18	

Table 1 contains a summary of these studies of megacolon by other authors, including a summarization of the changes noted in the myenteric plexus It shows that in 14 of the total of 18 cases for which data were collected from the literature there was absence of the ganglions of the myenteric plexus in the distal part of the colon or in a part of the colon not specified Six of the 18 were apparently definite cases of congenital megacolon, and in these there was absence of the myenteric plexus in the distal part of the bowel Evidence from the cases reviewed thus supports the previous hypotheses and experimental findings and shows that there is a disturbance of the normal autonomic innervation of the terminal segment of the colon in cases of megacolon and in particular in cases of congenital megacolon It has been our purpose to carry out a careful study of the myenteric plexus in a series of cases of congenital megacolon observed in one institution

SELECTION OF CASES

This report has been based on a study of 11 cases of congenital megacolon in the Section on Pathologic Anatomy of the Mayo Clinic. We were able to find 13 cases classified as cases of congenital megacolon. We were unable to study 2 of these accurately because of the fact that surgical removal of part of the colon had been performed and the portion of the colon available for our study was in several pieces, a circumstance which made identification from the anatomic standpoint impossible. These cases were eliminated from the study. All the cases fulfilled the criteria for congenital megacolon which we established for

TABLE 2—*Causes of Death in 10 Cases of Congenital Megacolon*

Cause	Cases
Malnutrition toxemia general debility	3
Spontaneous perforation of colonic ulcers	3
Postoperative peritonitis	2
Postoperative shock	1
Intestinal obstruction by huge fecalith	1
Total	10

TABLE 3—*Age Range of Patients Who Had Congenital Megacolon*

Age, Yr	No	%
Less than 5	5	46
5 to 9	2	18
10 to 19	1	9
20 to 29	3	27
Total	11	100

this study. Accurate definition of the type of case which was studied was felt to be essential. The criteria which we established for the diagnosis of congenital megacolon were (1) symptoms preferably present since birth, though cases were accepted in which the onset of symptoms was in early youth, (2) colonic dilatation and hypertrophy of a high grade, (3) maximal involvement present in the sigmoid colon, and (4) a typical clinical picture, which in essence was that bowel movements almost never occurred normally and the abdomen was huge, with palpable fecal masses, flaring costal margins, roentgenographic evidence of colonic dilatation and redundancy and the absence of a lesion on rectal, proctoscopic or general examination, that could cause obstruction

CAUSE OF DEATH

The cause of death was established at the time of postmortem examination in 10 of the 11 cases. In the eleventh case the specimen was obtained after subtotal colectomy, and the patient made an uneventful postoperative recovery.

Table 2 shows the causes of death in the 10 cases in which postmortem examination was performed. It is of importance to note that in 7 of these (70 per cent) the patient died from complications that occurred as a natural result of the disease and not as a result of surgical intervention. Volvulus, which is fairly frequent in cases of megacolon, was not observed in our series.

The age range of the patients who had congenital megacolon is shown in table 3. It can be seen that 64 per cent of the 11 patients were 9 years of age or younger. This is a general characteristic of any series of cases of true congenital megacolon. There were 10 males and 1 female, which is a greater proportion of males than usual. This fact is accounted for by the size of the series.

METHOD OF STUDY

The histologic study of the myenteric plexus in cases in which postmortem examination had been made presented certain problems which were not present in the subject have been performed.¹⁵ This allowed the use of spurravital staining technics and other methods which were not applicable in the study of tissues secured at necropsy and preserved in formaldehyde for periods varying from one to thirty years.

We have been unable to find a study of the myenteric plexus under comparable conditions which could be used to determine the normal findings in a routine necropsy series. As a corollary of the reported study, we have examined material in a series of 78 cases to determine the characteristics of the myenteric plexus of the colon and the normal variations in its distribution and staining. At the same time, we also decided on the staining methods to be used in the main study.

In our study of the series of cases used as controls, we utilized cases of peritonitis, intestinal obstruction and a wide variety of other conditions. To rule out the factor of selection, we incorporated in the control study a series of consecutive cases in which postmortem examination was performed. We have likewise studied for the sake of comparison a group of cases in which megacolon was secondary to obstructing lesions or considered to be acquired rather than congenital. The following are conclusions from the study of our series of control cases which are pertinent in the study of the myenteric plexus of the colon in cases of congenital megacolon.

- 1 Ganglions are present in practically every section taken from the colon.

- 2 So-called degenerative changes in the ganglion cells are commonly encountered in sections taken under the conditions of the study of the control cases and the cases of megacolon.

3 Nerve trunks (nonmyelinated) in the location of the myenteric plexus are extremely rare in the rectum and in other parts of the colon

4 Extreme dilatation of the colon has relatively little effect on the myenteric plexus apart from the fact that the ganglions seem to be somewhat more widely spaced than normal

5 Inflammatory changes in the colon have little effect on the myenteric plexus in the majority of instances

6 The rectum contained as many ganglions per unit of area as other parts of the colon or more

7 No separation of ganglion cells into Dogiel type I and type II could be made (a finding which has been described by Johnson^{15c}) This, however, may be due to the method of study that we used

8 The small cells in relation to nerve fibers and nerve cells we have called "supporting cells" Their exact nature has not been determined by us or others

The control study aided us in determining the staining methods which we would use in the study of the myenteric plexus of the colon under the conditions of the study as mentioned previously We found that the Bodian¹⁶ method of silver impregnation showed the nonmyelinated nerve fibers better than any other method and also showed the nerve cells of the ganglions well The Gros-Bielschowsky method¹⁷ of silver impregnation was used but was found to be satisfactory in a minority of the sections treated by this method The cresyl violet stain was found to be excellent for the study of the nerve cells The hematoxylin and eosin staining method was found to be of great general value, but the stains which were more specific in their action were frequently found to be necessary in our study We have also used connective tissue stains for certain sections, such as the Mallory-Heidenham, Mallory phosphotungstic acid and Van Gieson stains These were found to be of limited value

We took tissue blocks at frequent intervals in the parts of the colon that showed the greatest change in the myenteric plexus When these original sections were not adequate for a complete study we recut more blocks so that in each case there would be blocks cut from all the necessary locations to prove or disprove that the changes were as stated Each block was cut into four or more sections, and the silver impregnation methods of Gros-Bielschowsky and Bodian and the cresyl violet and hematoxylin and eosin stains were used on each The sections were cut

15 (a) Hill, C J VIII A Contribution to Our Knowledge of the Enteric Plexuses, Phil Tr Roy Soc, London, s B **215** 355-387 (June 15) 1927 (b) Dogiel, A S Zwei Arten sympathischer Nervenzellen, Anat Anz **11**:679-687, 1895-1896 (c) Lawrentjew, B I, and Sokolowa, M L Zur Lehre von der Cytoarchitektonik des peripherischen autonomen Nervensystems, Ztschr f mikr-anat Forsch **23** 527 (March) 1931 (d) Modern, F S, and Thienes, C H Vagal and Sympathetic Endings in the Rabbit Intestines, Science **83** 522 (May 29) 1936 (e) Johnson, S E Experimental Degeneration of the Extrinsic Nerves of the Small Intestine in Relation to the Structure of the Myenteric Plexus, J Comp Neurol **38** 299-314 (April) 1925 (f) Irwin, D A The Anatomy of Auerbach's Plexus, Am J Anat **49** 141-166 (Sept) 1931

16 Mallory, F B Pathological Technique A Practical Manual for Workers in Pathological Histology Including Directions for the Performance of Autopsies and for Microphotography, Philadelphia, W B Saunders Company, 1938, pp 228-229

1 mm or more apart, giving a serial section effect. In several of the cases we had a serial section of the entire part of the colon that would show any change in the myenteric plexus. The study of Irwin¹⁷ showed how unlikely it would be to miss the ganglions of the plexus completely in a section 2 cm long if the amount of plexus noted in his studies was present in 4 sq mm. Our series used in the control study adequately confirmed this, as we found no section in the hundreds that we studied in which we could not find nerve cells of the myenteric plexus.

We have not studied in detail the plexus of Meissner (submucous plexus) of the colon because the consensus¹⁸ is that its function depends on that of the myenteric plexus and also because its function is too poorly understood for a study to be of value. The subserous plexus, the deep muscular plexus of Drasch and Cajal and the internal plexus of Henle mentioned by some writers have not been studied for reasons similar to those stated for the exclusion of the submucous plexus. Also, owing to the location of the submucous plexus in the loose connective tissue of the submucosa, it would be difficult to be sure whether it was present or absent. The myenteric plexus was so confined in its usual location that there was no difficulty in determining accurately when it was present and when it was totally absent in any given section. In general we can tentatively state that the plexus of Meissner (submucous plexus) seemed to parallel the myenteric plexus in its presence or absence.

Figures 1, 2, 3 and 4 show the gross appearance typical of all the colons used in our study. We have primarily used the various anatomic sections of the colon to delineate the region from which the sections were taken. In 6 cases (54.5 per cent) there was a "normal" terminal segment of bowel, as compared with 57.7 per cent of a series of clinical cases reported by Whitehouse and others.¹⁹ In some cases this terminal segment which was normal or near normal in diameter was the rectum; in others the terminal segment was as high as the midsigmoid. We have not attempted to delineate accurately the anatomic bounds of this normal terminal segment in our cases. We have coined the term "transitional region" to apply to the part of the colon in which the maximally dilated bowel suddenly narrowed down to a terminal segment of normal size. The photographs of the gross specimens show this region clearly. We feel that the use of the term "transitional region" is worth while in the delineation of a particular part of the colon in which the myenteric plexus demonstrated a change in a good proportion of the cases studied.

In figures 1, 2 and 3 arrows point to the parts of the colon from which tissue blocks were removed for study. Some of the photomicrographs have the arrow number included in the legends so that reference can be made to the picture of the colon in the case referred to. We have included a few photomicrographs from control cases to demonstrate the usual appearance of the myenteric plexus to be contrasted with the photomicrographs of the sections in which no myenteric plexus is present.

We have reported 5 of the 11 cases in relatively complete fashion and the other 6 briefly. The similarity of the cases was so marked that an accurate description of the customary clinical and pathologic findings seemed to be given adequately in the 5 cases selected for detailed presentation.

17 (a) Mallory¹⁸ pp 227-228 (b) Kernohan, J. W. Preparation of Neurological Material for Histologic Study, *Am J Clin Path* 4:410-425 (Sept.) 1934

18 Babkin, B. P. Secretory Mechanism of the Digestive Glands, New York, Paul B. Hoeber, Inc., 1944, p 125. Etzel.¹⁹

RESULTS OF STUDY OF THE MYENTERIC PLEXUS IN CASES
OF CONGENITAL MEGACOLON

Table 4 demonstrates the most important finding made in the study of the myenteric plexus in 11 cases of congenital megacolon. In 100 per cent of the cases studied there was an absence of the ganglions of the myenteric plexus (fig 5) in the terminal portion of the colon. In all cases there were ganglions of the myenteric plexus present in the descending colon, transverse colon, ascending colon and cecum. There

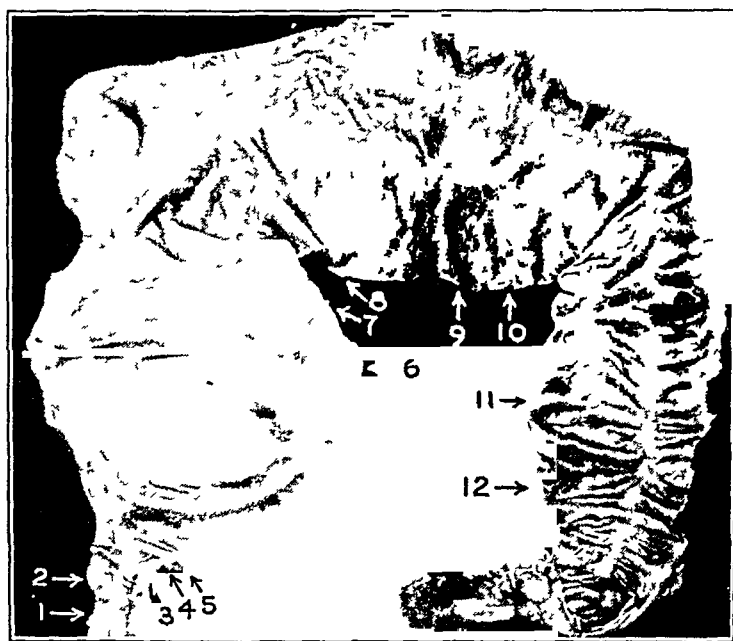


Fig 1—Typical maximal involvement of sigmoid, rapid change to normal rectum and gradual diminution of size toward cecum. Locations from which blocks of tissue were taken for histologic examination are marked by arrows. Areas 1 through 6 contained no ganglions, 7 and 8 contained a few and 9 through 12 contained a moderately diminished number as compared with the normal.

was thus a change in the myenteric plexus that occurred distal (toward the cecum being proximal and toward the rectum distal) to the descending colon in every case. In 80 per cent of the cases in which there was a definite transitional region (defined in the section "Method of Study") there was absence of the ganglions of the myenteric plexus from the rectum into the transitional region. In 60 per cent of the cases there was absence of the ganglions of the myenteric plexus down to and including the rectum in the distal segment of the sigmoid; which we considered to begin just proximal to the transitional region. In 20 per cent of the cases studied there was absence of the ganglions of the myenteric plexus in the proximal segment of the sigmoid, in the lower part of the descending colon and in all parts distal to them. By absence of the

ganglions of the myenteric plexus we mean that we were unable to find a single identifiable ganglion cell in any part of any section from the region mentioned

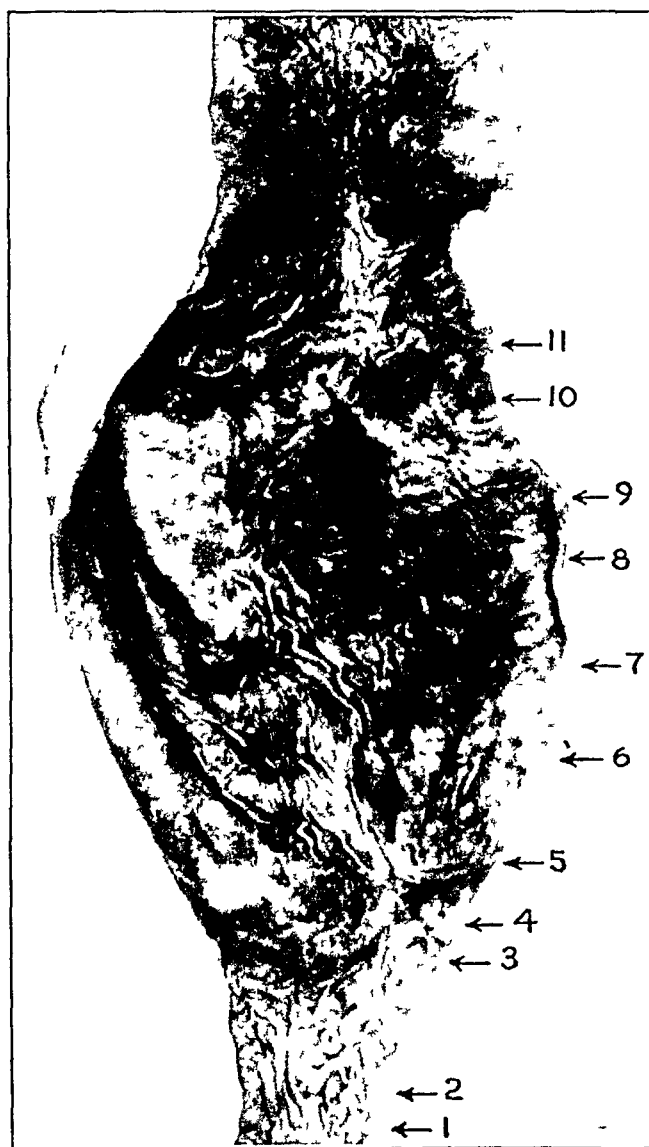


Fig 2—Dilated sigmoid and normal rectum. Locations from which blocks of tissue were taken for histologic examination are marked by arrows. Areas 1 through 7 contained no ganglions, 8 contained a few nerve cells and 9 through 11 contained a normal number of ganglions.

Figures 6 and 7 demonstrate graphically the absence of the myenteric plexus and should be contrasted with figure 8, which demonstrates the normal myenteric plexus. Figures 6a and 8a should be compared with each other. They are of approximately the same magnification, and the stain in both instances is by the Bodian method. The areas shown are

comparable. The absence of the myenteric plexus is thus seen to be striking. The different thickness of muscle walls can also be seen. One important question cannot be entirely answered, which is, how close to the anal sphincter does the absence of the myenteric plexus extend? In several cases the specimen included perianal skin, and in these cases there was no myenteric plexus in the terminal portion of the rectum. We feel that, with the necropsy technic used, we were able to study all but the terminal few centimeters of the rectum in all our cases, and since there was no evidence of the myenteric plexus being present in

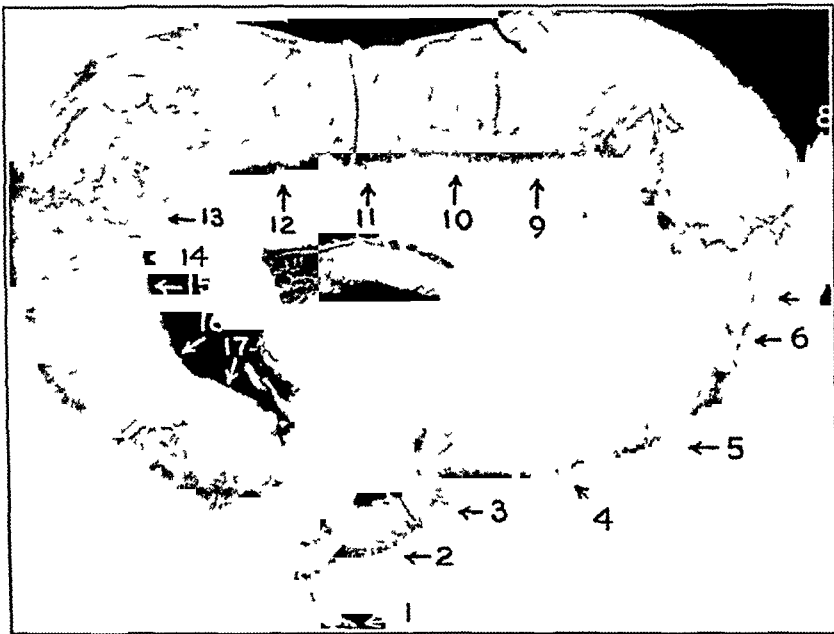


Fig. 3—Segment of bowel in center is normal colon for comparison. Locations from which blocks of tissue were taken for histologic examination are marked by arrows. Areas 1 through 4 contained no ganglions, 5 through 7 contained a few and 8 through 17 contained a normal number. Note the normal size of the rectum.

the terminal portion of the rectum in the several cases in which we had complete specimens, it is likely that the changes which we have described are present over the entire terminal segment down to the anal sphincter.

A second observation was made in the study of the 11 cases of congenital megacolon, which we can find described only once previously.^{4b} In every case studied there was the presence of nonmyelinated nerve trunks between the longitudinal and circular muscle layers in the distal part of the colon. These were not present in the series of cases used as controls, and hence we considered these nerves to be a definite part of the pathologic changes of congenital megacolon. The nonmyelinated nerves were not present to any pronounced degree in the part of the colon which contained ganglions of the myenteric plexus but

were always in the part of the colon in which no ganglions of the myenteric plexus could be demonstrated. These nerves are not to be confused with nerve fibers which are seen in relation to the ganglions in the normal plexus. The nerves which we have described are closely



Fig. 4—Specimen of colon in figure 3 opened in rectosigmoid region. The abrupt transition from the sigmoid to the normal rectum is characteristic. The portion of the colon between the two extremes in size we have called the 'transitional region'.

packed bundles of nonmyelinated nerve fibers with a definite connective tissue sheath. The size of the nerves varied considerably in individual cases and particularly from case to case. Figures 9 and 10 *a* show the nerves seen in 3 of the cases of megacolon. The variation in size, the connective tissue sheath, the location in the usual site of the myenteric plexus and the entrance into the colon, as noted in figure 10 *a* in company with the blood vessels can be well observed. Some of the nerves

were smaller and some were larger than the ones demonstrated in the figures. We are unable to state the part (sympathetic or parasympathetic) of the autonomic nervous system represented by these nerves, hence their significance is unknown to us.

Early in our study we were confronted with the question of degenerative changes in the nerve cells. This question can be answered,

TABLE 4—*Sites in Which Ganglions of Myenteric Plexus Are Absent**

Case	Rectum	Transition il Region	Sigmoid		Descending Colon	Transverse Colon	Ascending Colon	Cecum
			Distal	Proximal				
1	0	0	0	0	+	+	+	+
2	0	0	0	+	+	+	+	+
3	0	x	0	+	+	+	+	+
4	0	x	+	+	+	+	+	+
5	0	0	+	+	+	+	+	+
6	0	x	0	+	+	+	+	+
7	0	+	+	+	+	+	+	+
8	0	x	x	x	+	+	+	+
9	0	x	+	+	+	+	+	+
10	0	x	0	0	+	+	+	+
11	x	0	0	+	+	+	+	+
% with absence	100	80	60	20	0	0	0	0

*0 Signifies absent, + present and x section not available

TABLE 5—*Plexus of Auerbach in Cases of Secondary Megacolon**

Case	Cause	Rectum	Sigmoid	Descending Colon	Transverse Colon	Ascending Co lon and Cecum
12	Carcinoma of rectum	+	+	+	+	+
13	Carcinoma of sigmoid	+	+	+	+	+
14	Carcinoma of rectum	+	+	+	+	+
15	Volvulus	+	+	+	+	+
16	Enterocolitis	+	+	+	+	0

*0 Signifies absent and + present

as noted previously, from the study made on the cases used as controls. The series of cases used as controls and the series of cases of congenital megacolon demonstrated the same "degenerative" changes to such a degree that we have concluded that none of these should be reported as part of the pathologic changes which occurred in congenital megacolon. Even under the best of conditions it would be difficult to be sure that changes present in the myenteric plexus were not due to age of the specimen, fixation, sectioning or staining.

Cameron^{4t} expressed the opinion that inflammatory changes in the myenteric plexus are important in the causation of megacolon. In our study we looked carefully for such changes, but in our cases there was no evidence of recent or old inflammatory change in the myenteric plexus. In fact, we noted that even in the presence of active suppurative colitis, chronic ulcerative colitis and similar conditions there was an "immunity"

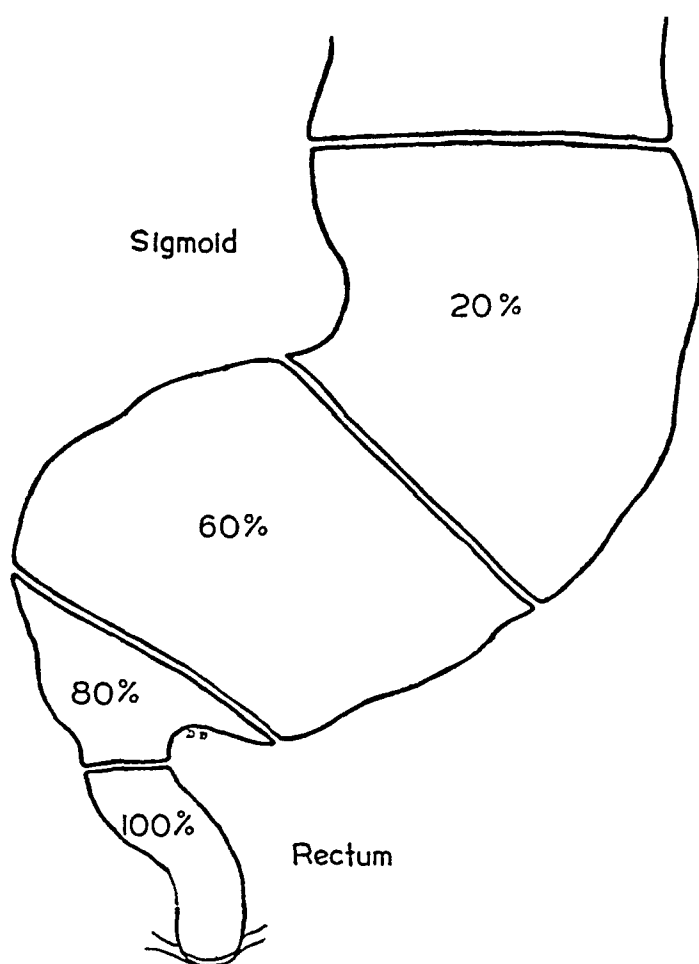


Fig 5—Percentage of cases in which the myenteric plexus was absent from the terminal part of the rectum to the indicated level. A rectum of normal size as seen in the majority of cases is shown.

from such involvement of the myenteric plexus. It is our opinion, in view of the study, that we have no evidence which would suggest or support the hypothesis of inflammatory damage to the myenteric plexus.

In view of the fact that we have described a part of the colon in which the ganglions of the myenteric plexus were absent and another part of the colon in which the ganglions were present in more or less

normal numbers, the microscopic changes in the "no man's land" between the regions mentioned would be of interest. The accuracy of any statements made without serial sections would be exposed to criticism, but we felt that our study justified the statement of certain generalities in this regard.

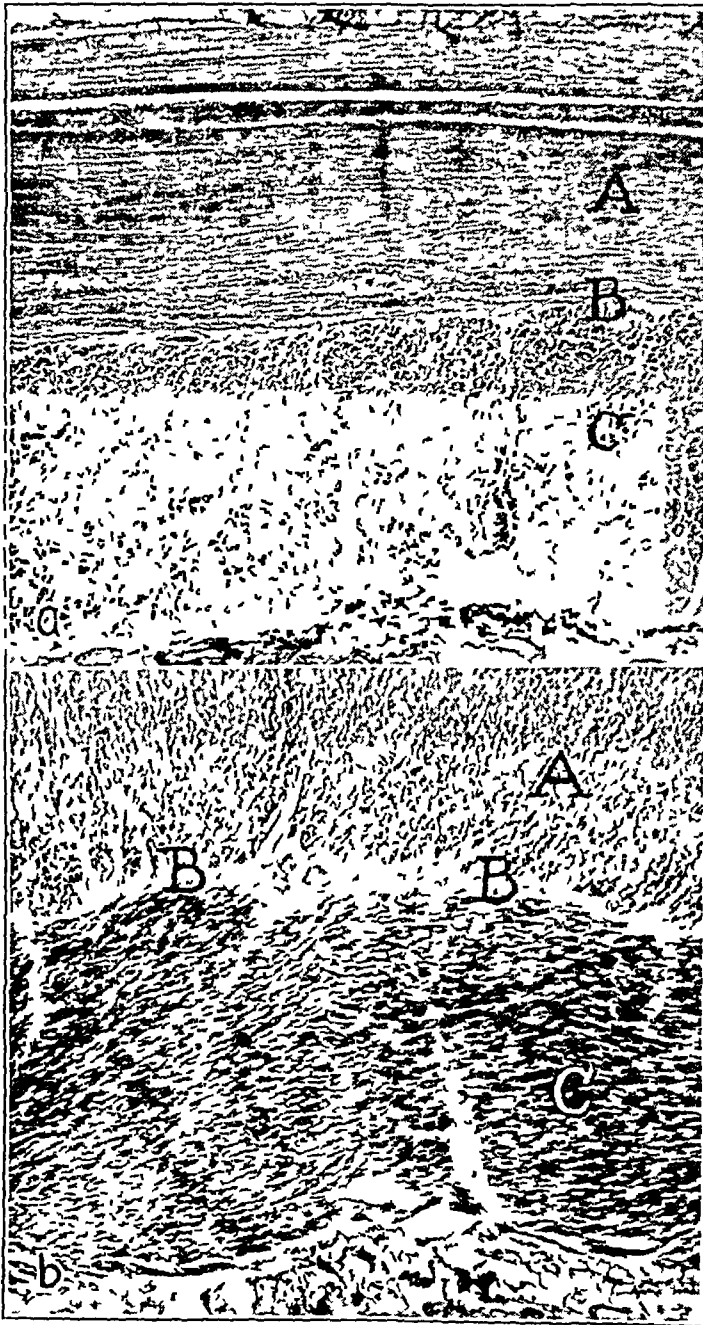


Fig 6—*a*, absence of myenteric plexus in transitional region (from areas 3, 4 and 5 in figure 1) *A*, longitudinal muscle, *B*, usual site of myenteric plexus, *C*, circular muscle (Bodian stain, $\times 55$), *b*, absence of myenteric plexus in rectum (from areas 1 and 2 in figure 2) *A*, longitudinal muscle, *B*, usual site of myenteric plexus, *C*, circular muscle (Bodian stain, $\times 60$)

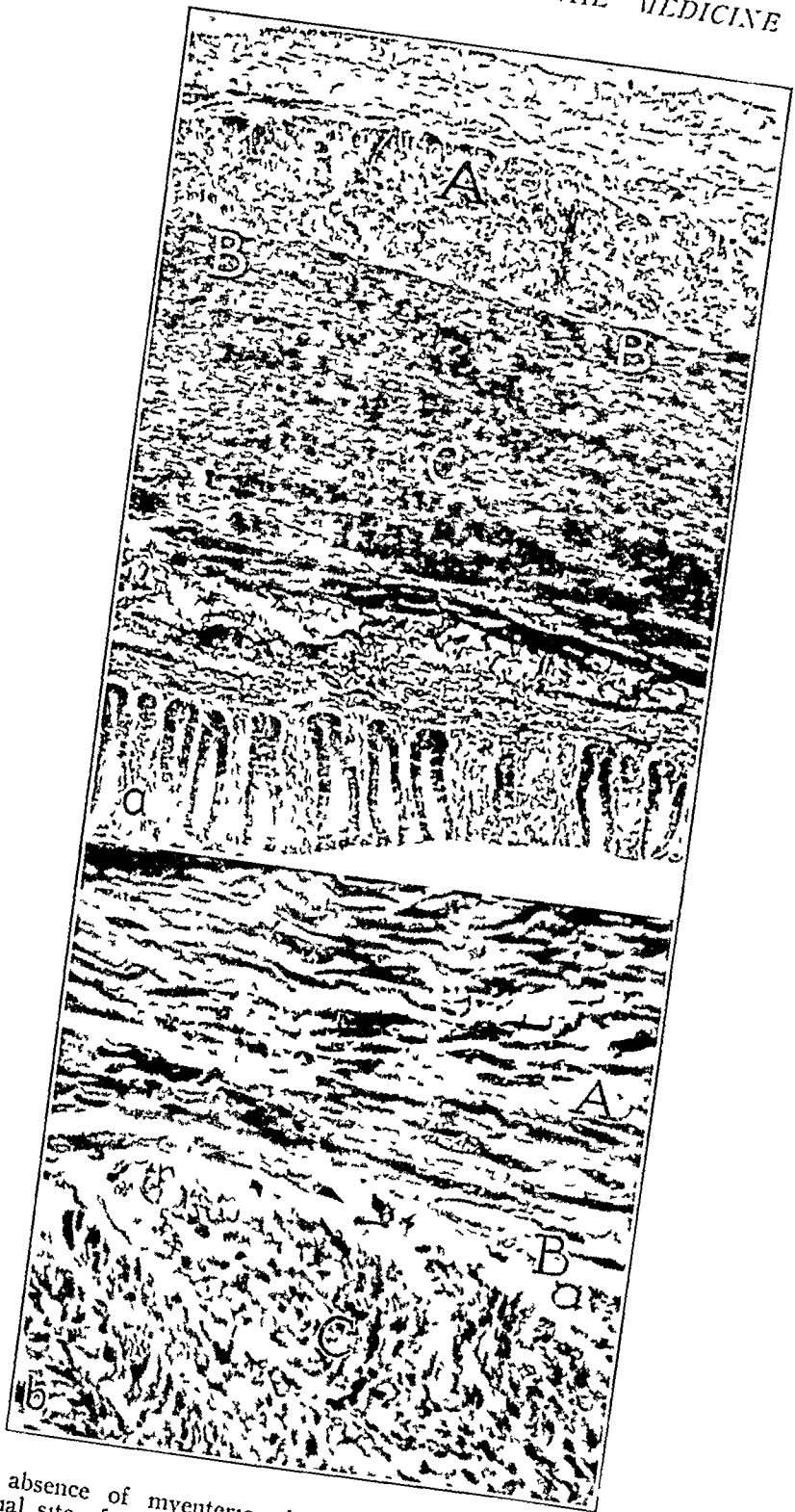


Fig 7—*a*, absence of myenteric plexus of sigmoid colon *A*, longitudinal muscle, *B*, usual site of myenteric plexus, *C*, circular muscle (Bodian stain, $\times 50$), *b*, absence of myenteric plexus of rectum *A*, longitudinal muscle, *B*, usual site of plexus, *C*, circular muscle (Bodian stain, $\times 275$)

For the sake of simplicity, we have separated the 11 cases of congenital megacolon under three rough categories. The most common finding was a quick change to a relatively normal myenteric plexus in the colon proximal to the region in which the ganglions of the myenteric plexus were absent. It was our impression that in several cases of this

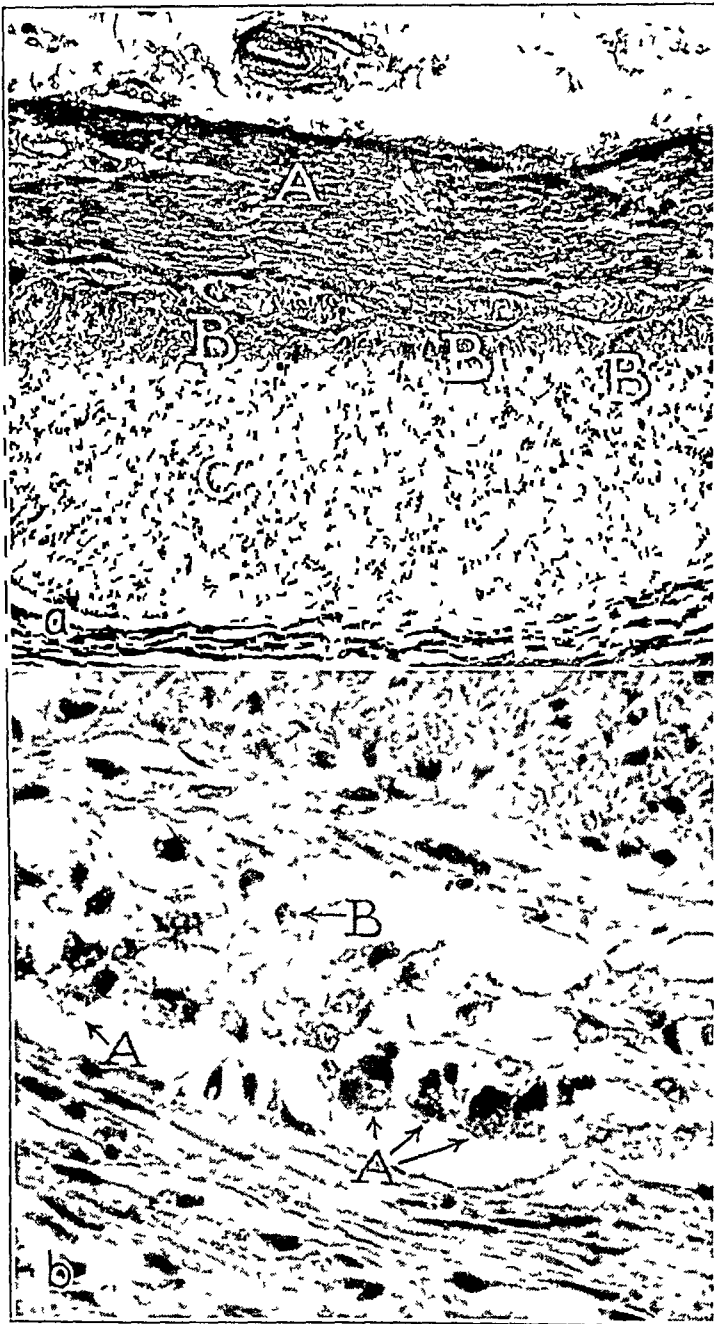


Fig 8—*a*, customary distribution of myenteric plexus in rectum from control series. Plexus is well demarcated in zone between longitudinal and circular muscle layers. *A*, longitudinal muscle, *B*, ganglions, *C*, circular muscle (Bodian stain, $\times 50$) *b*, normal ganglion from case in control series. Compare with figure 11*b*. *A*, nerve cell, *B*, supporting cell (hematoxylin and eosin, $\times 425$)

group the change to a relatively normal plexus occurred in the space of a few centimeters. This was considered to be true in 5 of the 11 cases studied. The next most common finding was the presence of a few scattered ganglions in the segment of colon proximal to the part that showed no ganglions of the myenteric plexus. Next to this segment there



Fig 9—*a*, nerve trunk in rectum (nonmyelinated) *A*, circular muscle, *B*, nerve trunk, *C*, longitudinal muscle (Bodian stain, $\times 200$), *b*, nonmyelinated nerve trunk in rectum between longitudinal and circular muscle layers *A*, nerve trunk, *B*, longitudinal muscle, *C*, circular muscle (Bodian stain, $\times 120$)

was a gradual increase in the number of ganglions and an improvement in their general appearance until a relatively normal myenteric plexus was seen in 4 of the 11 cases studied. The least common finding, noted in 2 of the 11 cases, was the presence of a few ganglions and then a gradual increase in the number in a spotty fashion, with some areas that contained few ganglions. No areas of the colon in these cases were

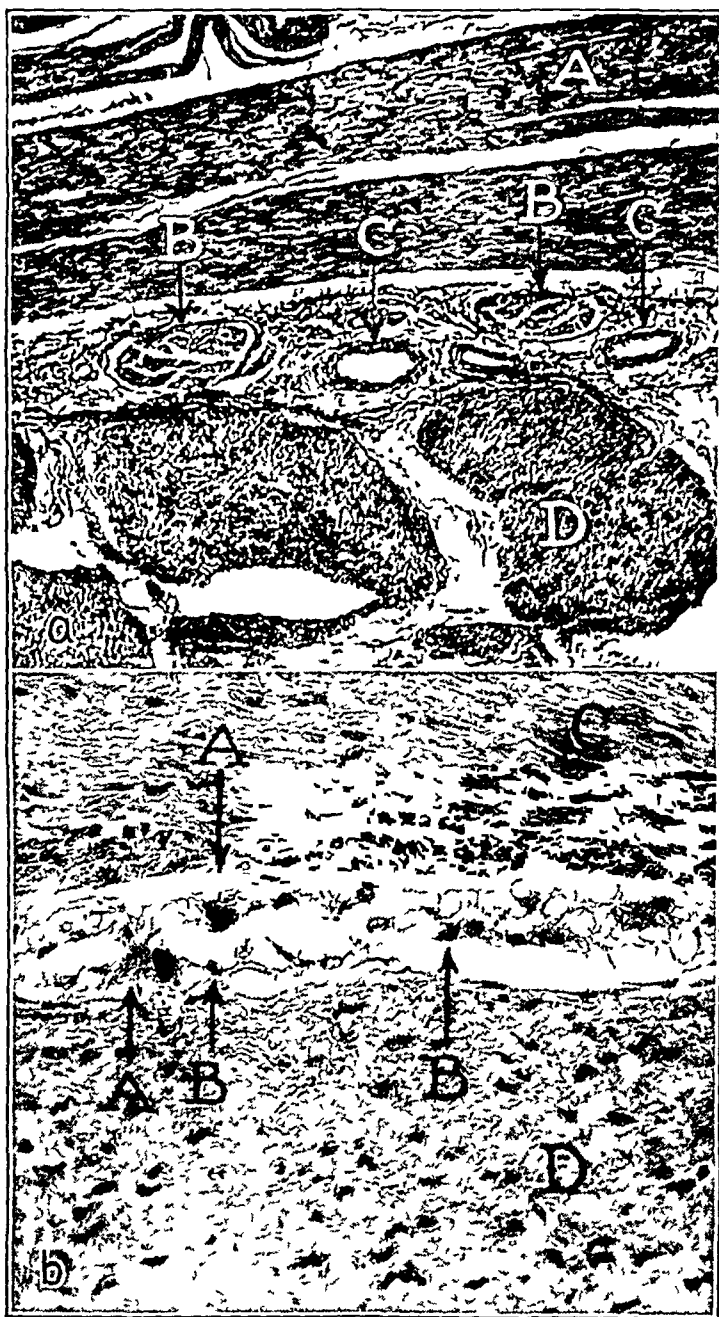


Fig 10—*a*, ganglions absent. Nerve trunks in relation to small blood vessels in rectum. *A*, longitudinal muscle, *B*, nerve trunks, *C*, blood vessels, *D*, circular muscle (hematoxylin and eosin, $\times 90$), *b*, ganglion in ascending colon (from area 11 in figure 1). *A*, nerve cell, *B*, supporting cell, *C*, longitudinal muscle, *D*, circular muscle (hematoxylin and eosin, $\times 200$)

seen to contain a normal plexus. Figures 10 *b* and 11 *a* demonstrate normal ganglions (not from the terminal segment of the colon) which are similar to those seen in the series of cases used as controls. Figure 11*b* demonstrates a ganglion similar to many other ganglions thus

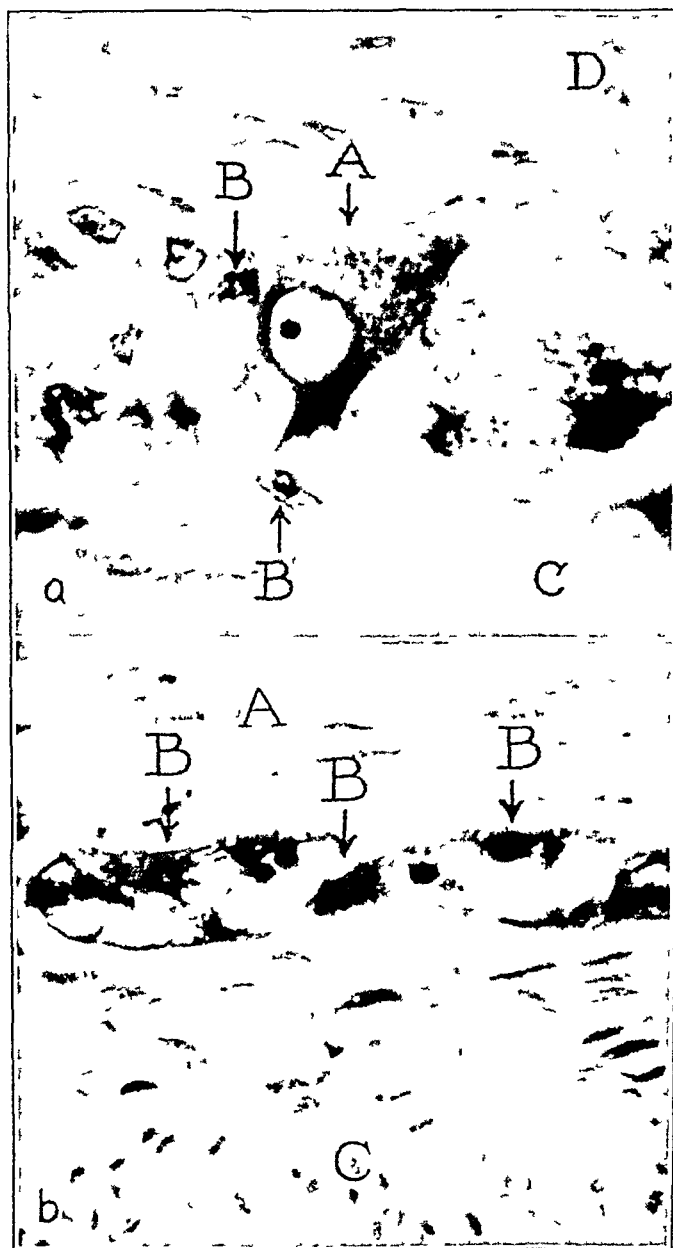


Fig 11—*a*, ganglion of transverse colon. Normal nerve cell and a number of supporting cells. Four blurred nerve cells are also present. *A*, nerve cell, *B*, supporting cell, *C*, circular muscle, *D*, longitudinal muscle (cresyl violet, $\times 880$). *b*, ganglion of descending colon. Normal number of nerve cells, few supporting cells and nerve fibers. Compare with figure 8 *b*. *A*, longitudinal muscle, *B*, nerve cells, *C*, circular muscle (Gros-Bielschowsky stain, $\times 415$).

located, from the 'no man's land' of change in the myenteric plexus. In comparison with figure 11 from the control series, with which it is comparable in magnification, it can be seen that there are few supporting cells or nerve fibers, definite 'atrophy' and a general failure to reach the standard of architecture set by the normal ganglion shown in figure 8 b. This is considered to be a characteristic ganglion of the region in which the change from no ganglions to a normal or a diminished number occurred. Many such ganglions showed only one to three nerve cells and hence were much smaller than the average seen in the series of cases used as controls.

REPORT OF CASES

CASE 1—A 15 year old boy was seen on Oct 27, 1941, because of constipation and general debility. Since birth there had been considerable difficulty in getting his bowels to move. He had been treated with anal dilation and enemas, with some improvement. Abdominal distention and constipation continued at intervals, and daily enemas were required during certain periods. During the six months prior to his admission to the clinic, increasing difficulty in passing gas, constipation and pronounced abdominal distention had been noted. The patient had also noted fatigability, anorexia, loss of weight and pallor.

Physical examination showed a thin, pale, white boy with an enlarged and tightly distended abdomen. The costal margins showed a pronounced flaring. The height of the patient was 62 inches (157 cm) and his weight was 99 pounds (44.9 Kg). The blood pressure was 140 mm of mercury systolic and 90 diastolic, the pulse rate was 88 beats per minute and the oral temperature was 98.9 F. The abdomen was tense and was doughy to palpation. An easily discernible outline of the bowel was seen under the thin abdominal wall. Rectal examination revealed an empty rectum which was markedly encroached on by an extrarectal mass (feces). Sigmoidoscopic examination revealed a normal mucosa, with the caliber of the bowel seemingly larger than normal. Roentgenographic and roentgenoscopic examination of the colon confirmed the diagnosis of megacolon.

The condition of the patient became worse after his admission. Progressive abdominal distention ensued, and this did not respond to medical treatment. A huge fecalith was present in the sigmoid colon, and it was the clinician's opinion that this was the cause of the partial obstruction of the colon. Emergency colostomy was performed, but this was without beneficial effect. Death occurred on Nov 2 1941.

Postmortem examination revealed an emaciated boy with a greatly distended abdomen, the circumference of which was 97 cm at a level just above the umbilicus. The circumference of the chest was 80 cm at the level of the nipple line. The apexes of the diaphragm were at the third rib on the right and the fourth rib on the left. The peritoneal cavity revealed no peritonitis and was entirely filled by the tremendously distended and hypertrophied colon, which had pushed the urinary bladder anterior to the symphysis pubis. There was atelectasis of grade 3 (on the basis of 1 to 4, 1 being the least) of the lower lobes of the lungs. The esophagus, stomach, duodenum and jejunum were grossly normal. The ileum revealed a grade 1 (basis of 1 to 4) dilatation of the last 30 cm of its length. The dilatation of the colon (fig 1) was maximal in the sigmoid region, with a circumference of 42 cm in this location. Proximal to the sigmoid there was a gradual diminution of the size of the bowel to the cecum and then there was slight dilatation of the

terminal 30 cm of the ileum The wall of the descending colon and sigmoid was 0.3 cm thick The wall of the ascending colon and cecum was thin The bowel distal to the rectosigmoid junction was normal in diameter and thickness There was no point of obstruction noted The mucosa throughout the colon was markedly congested, particularly in the sigmoid The kidneys revealed a grade 1 (basis of 1 to 4) dilatation of the pelvis, calices and ureters on the left and a dilated pelvis and calices of grade 2 and urethral dilatation of grade 1 on the right

*Microscopic Study*¹⁹—Tissue blocks were taken from two levels of the non-dilated rectum (arrows 1 and 2, fig 1) Examination of sections from these blocks showed no nerve cells, supporting cells or architectural remains of the plexus There were small nerve bundles at intervals, composed of nonmyelinated nerve fibers

Blocks taken from three levels of the region of transition (arrows 3, 4 and 5, fig 1) showed no nerve cells (fig 6 a) In the usual location of the plexus of Auerbach there was a narrow region of collagen interrupted at intervals by nerve trunks Sections taken from the level of greatest colonic dilatation (arrow 6, fig 1) showed no definite nerve cells although there were small, thin groups of supporting cells and nerve fibers at intervals in the usual location of the ganglions These cells were rather argentophilic Blocks taken from two levels of the descending colon (arrows 7 and 8, fig 1) showed scattered ganglions which contained one to five nerve cells each There was a normal arrangement of these ganglions, and the nerve pathways between them were present There were few supporting cells noted in the distal section of the descending colon The proximal section of the descending colon showed the same diminution of nerve cells, but a normal number of supporting cells was seen Variation in staining with cresyl violet was observed, with some cells appearing dark and others with apparent lack of Nissl substance Blocks taken from two levels of the transverse colon (arrows 9 and 10, fig 1) showed ganglions and fibers to be moderately diminished quantitatively All methods of staining showed an irregularity in outline and staining of the nerve cells, with indistinct nuclei and an impairment of the usual regularity of the cytoplasm This was in spite of the normal appearance of the mucosa and other tissues, which probably demonstrated proper fixation, preservation and staining of the tissues A block from the ascending colon (arrow 11, fig 1) showed a sparsity of the ganglions, which, however, were normal in appearance (fig 10 b) A block from the cecum (arrow 12, fig 1) showed a similar appearance, after microscopic study, to that of the ascending colon

Summary—There was an absence of the ganglions of the myenteric plexus in the rectum and the sigmoid colon in this case Beginning at the level of the descending colon there were scattered ganglions which contained a few nerve cells They became more numerous as sections from more proximal segments of the colon were examined, although atrophy and "thinning out" of the plexus was definite in the remainder of the colon

19 Unless otherwise noted, each block was made into four tissue sections cut at a distance of 1 mm apart, which gave a serial section effect The cresyl violet, hematoxylin and eosin, Bodian and Gros-Bielschowsky methods of staining were used Also in the description, unless otherwise stated, all nerve fibers are nonmyelinated, and the word "plexus" means the myenteric plexus The regions described in each section will be generally understood to be confined to the space between the longitudinal and circular muscle bundles of the colon, where the myenteric plexus is normally located

CASE 2—A 6 year old boy was seen on May 5, 1932, because of the diagnosis, made elsewhere, of Hirschsprung's disease. At the time of birth the child was noted to have a large abdomen. The birth weight was 8 pounds and 3 ounces (3.7 Kg), and the subsequent development was considered normal. "Stoppage of the bowels" every few months since birth had been noted by the parents of the patient. At such a time abdominal distention and vomiting were noted. Enemas were given, with eventual improvement of the individual episodes of distention. A particularly severe attack of obstipation at the age of 2½ years had necessitated hospitalization. The patient had had colonic irrigations frequently since then. Cramping abdominal pains were noted during some of the attacks of obstipation. Progressive difficulty in keeping the bowels open had been noted by the parents.

Physical examination revealed a poorly developed and nourished white child, whose height was 43 inches (109 cm) and whose weight was 45 pounds (20.4 Kg). The blood pressure was 110 mm of mercury systolic and 75 diastolic, the pulse rate was 136 beats per minute and the rectal temperature was 99.4 F. The tonsils were enlarged and chronically infected, and there was dental caries. The abdomen was protuberant, and distended loops of bowel packed and distended with feces were palpable. The rectum was not enlarged from the anus to the level of the rectosigmoid juncture. Laboratory studies showed the concentration of hemoglobin to be 16.9 Gm per hundred cubic centimeters of blood, erythrocytes numbered 5,200,000 and leukocytes 9,800 per cubic millimeter of blood. A roentgenogram showed the chest to be normal. Roentgenographic and roentgenoscopic examination of the colon by means of barium and air showed notable distention of the entire colon above the rectum.

The patient was hospitalized and prepared for sympathectomy by means of daily enemas of diluted hydrogen peroxide, diathermy to the abdomen and oil retention enemas. There was an initial loss of 7 pounds (3.2 Kg) at the time that the colon was partially cleared of its fecal contents, but the child regained 5 pounds (2.3 Kg) of his body weight prior to operation. Lumbar ganglionectomy was performed, the second, third and fourth lumbar sympathetic ganglions being removed bilaterally. The presacral nerves were also resected. At this time the large intestine was seen to be 8 inches (20 cm) in diameter, and the maximal colonic involvement was that of the proximal two thirds of the lower part of the colon and the distal third of the transverse colon. The patient died on the operating table.

Postmortem examination revealed the body of a thin, poorly developed child which measured 115 cm in length and weighed 46 pounds (20.9 Kg). The abdomen was greatly distended, and a recent midline incision was noted. The apexes of the diaphragm arched to the third interspaces bilaterally. When the abdomen was opened, the colon was seen to fill the entire abdomen and there was colonic dilatation of grade 4. The colon demonstrated a segmental type of megacolon, being normal from the cecum to the left third of the transverse colon, where thickening and dilatation appeared, and then extended to the upper point of the rectum where the dilatation ended abruptly (fig 2). The colon at the point of maximal dilatation was 3 to 4 mm thick. There was a diameter of 20 cm at the point of maximal dilatation. The rectum was not dilated or thickened. The esophagus, stomach, small bowel, kidneys, pelves, ureters and bladder were grossly normal.

Microscopic Study—Blocks from two levels of the normal rectum (arrows 1 and 2, fig 2) showed no elements of the plexus (fig 6 b). Nerve trunks were present (fig 9 a). Blocks from three parts of the region of transition (arrows

3, 4 and 5, fig 2) from nondilated to dilated bowel showed no plexus. Blocks from two levels of the dilated sigmoid (arrows 6 and 7, fig 2) showed that there was no plexus present in the distal segment of the sigmoid. A block from the sigmoid more proximal to this (arrow 8, fig 2) showed a marked sparsity of plexus, with single nerve cells in several places and a few nerve fibers but no other structures of the plexus. Blocks taken from three levels above this (arrows 9, 10 and 11, fig 2) showed an apparent sudden change to a normal plexus. Blocks from six levels of the descending colon, transverse colon, ascending colon and cecum showed a plexus that was within normal limits.

Summary—Seven blocks from the rectum, region of transition and dilated sigmoid showed a complete absence of the myenteric plexus. In the colon proximal to the sigmoid there was a striking paucity of nerve cells and then a rather sudden change to an apparently normal plexus.

CASE 3—A 5 year old boy was seen on Nov. 3, 1937 because of the complaint of "no bowel movements without help since the age of three days." The child weighed $8\frac{3}{4}$ pounds (3.9 Kg.) at birth and was a full term baby. Development had been considered normal, the weight at the age of 1 year being 21 pounds (9.5 Kg.). Ever since birth bowel movements had been "rocklike" and "very few and far between." Enemas were given twice weekly, and spontaneous bowel movements occurred less than once a month. During the year previous to the time the child was brought to the clinic there had been an increase of abdominal distention. Attacks of distention had been associated with vomiting and low fever.

Physical examination showed a poorly developed and nourished child whose height was 42 inches (107 cm.) and whose weight was 43 pounds (19.5 Kg.). The blood pressure was 118 mm. of mercury systolic and 70 diastolic, the pulse rate was 108 beats per minute and the rectal temperature was 99.4 F. The abdomen was markedly distended, nontender and relaxed, and huge peristaltic waves covering a third of the abdomen were noted. There was no spasm of the rectal sphincter. Laboratory studies showed the concentration of hemoglobin to be 13.1 Gm. per one hundred cubic centimeters of blood, erythrocytes numbered 4,600,000 and leukocytes 10,300 per cubic millimeter of blood. The differential count of the leukocytes was within normal limits. A roentgenogram showed the chest normal, and roentgenographic and roentgenoscopic examination of the colon showed a megacolon with a large opaque residue present in the dilated bowel.

The patient was hospitalized and was given Learmonth's pills (active ingredient, eserine), diathermy to the abdomen, desiccated thyroid, enemas, saline cathartics and a residue-free diet. A large fecalith, which was palpable through the anterior abdominal wall, was present in the colon. The child did not improve during the course of treatment and suddenly became quite toxic for no apparent reason and died within a few hours after the first signs of toxicity.

Postmortem examination revealed a thin child, 108 cm. long and weighing 40 pounds (18.1 Kg.). There was considerable generalized abdominal distention. When the abdomen was opened, the omentum was seen to be paper thin and stretched over the hugely distended colon. There was no peritoneal fluid present in the abdominal cavity, and the peritoneal surfaces were smooth and glistening. The apexes of the diaphragm arched extremely high bilaterally. The colon was dilated (4 plus) except for the rectum and lower part of the sigmoid, where an abrupt change from dilatation to a normal caliber of the bowel occurred (figs 3 and 4). The wall of the colon was markedly thickened. The esophagus, stomach, small intestine, kidneys, pelves, ureters and bladder were grossly normal.

Microscopic Study—Blocks were taken from three levels of the nondilated portion of the rectum (arrows 1, 2 and 3, fig 3) The lowest section showed several branches of a myelinated nerve trunk and there were nonmyelinated nerve fibers running in groups, constituting a nonmyelinated nerve bundle (fig 9 b) This was not similar to the usual appearance of nonmyelinated nerve fibers between the ganglions of the normal rectum These nonmyelinated nerves entered or left the colon in relation to the blood vessels and were present between the longitudinal and circular muscle coats of the colon (fig 10 a) No nerve cells, groups of supporting cells or spaces were seen that would be indicative of the presence of the myenteric plexus Blocks were taken from two levels of the dilated sigmoid (arrows 4 and 5, fig 3) The distal section (arrow 4 fig 3) showed no nerve cells, ganglions, supporting cells or spaces (fig 7a) The proximal section showed six ganglions, each containing two to five nerve cells, no supporting cells of note and few nerve fibers The nerve cells were smaller than normal and lacked clarity, and some had an unusual affinity for cresyl violet There was a definite paucity of ganglions Blocks were taken from three levels of the descending colon (arrows 6, 7 and 8, fig 3) One block showed a moderate diminution of the number of ganglions There was also decided diminution of the number of interganglionic nerve fibers The majority of the nerve cells showed a spotty distribution of Nissl substance and a ragged outline There were few supporting cells The second block showed only two identifiable nerve cells in one section The third block (fig 11 b) showed an almost normal number of ganglions but few supporting cells or interganglionic fibers Blocks were taken from four levels of the transverse colon (arrows 9 through 12, fig 3) One block showed a normal number of nerve cells, supporting cells and nerve fibers but there was an unusual variation in the affinity of the nerve cells for the silver impregnation methods The other blocks varied somewhat in the number of ganglions yet no definite abnormality was noted Blocks taken from three levels of the ascending colon (arrows 13, 14 and 15, fig 3) showed no essential variation of the ganglions from normal (fig 11a) Blocks taken from two levels of the cecum (arrows 16 and 17, fig 3) showed no essential variation from normal

Summary—The change from the absence of plexus to a normal plexus occurred in the dilated sigmoid There was a gradation from an absence of plexus to a normal plexus, this gradation consisted of a paucity of ganglions, nerve cells, supporting cells and nerve fibers and apparent diminution in the size of the nerve cells

CASE 4—A 2 year old boy was seen on May 12, 1943, because of the parents' complaint that he "won't eat and has had bloating since birth" When the baby was 3 days old, the parents noted that his bowels had not moved Castor oil was administered, without a resulting bowel movement Diarrhea was noted during the second and third weeks of life, at this time as many as six stools were observed in a day The child had subsequently been in poor health Nursing was poor, and the feedings were frequently vomited in the early days of life Some improvement in these symptoms was subsequently noted The abdomen was distended from time to time An attack of whooping cough at the age of 4 months was extremely severe, and the parents felt that the bowels had been even more constipated since that time, with an occasional severe attack of abdominal distention being noted The stools were occasionally foul and foamy but usually were hard and inspissated

Physical examination showed the baby to have the appearance characteristic of marasmus, with severe abdominal distention, clubbing of the fingers and toes and thrush of the oral mucous membrane The rectal temperature was 102 F The abdomen was distended by loops of large bowel, the outlines of which were

visible through the thin abdominal wall. Laboratory studies showed the concentration of hemoglobin to be 6.2 Gm per hundred cubic centimeters of blood, erythrocytes numbered 3,080,000 and leukocytes 11,900 per cubic millimeter of blood. Differential count of the leukocytes showed 27 per cent lymphocytes, 8 per cent monocytes, 16 per cent stab forms and 49 per cent mature forms of neutrophilic leukocytes. The study of the blood smear showed anisocytosis, hypochromasia, a left shift and toxic changes in the polymorphonuclear leukocytes.

The patient did not respond well to medical treatment and died three days after admission to the hospital. The opinion of the attending physician was that death was attributable to general weakness and debility.

Postmortem examination revealed an infant who was 76 cm long, weighed 12 pounds (5.4 Kg) and was emaciated (3 plus). The panniculus adiposus measured 3 mm in thickness. The chest was barrel shaped, with a wide flare of the lower portion. The abdomen was greatly distended, and when it was opened the colon was noted to be hypertrophied and markedly dilated down to the rectum, which was of normal diameter. The peritoneal cavity contained 50 cc of clear fluid. The esophagus, stomach, small bowel, kidneys, pelvis, ureters and bladder were grossly normal.

Microscopic Study—Blocks from the rectum were stained with hematoxylin and eosin, Bodian, cresyl violet, Mallory-Heidenham, Mallory phosphotungstic acid, Verhoeff's elastic, Van Gieson and mucous stains. No nerve cells were seen, and no normal nerve fibers were noted. Blocks from six levels of the sigmoid contained nerve cells and nonmyelinated nerve fibers. The more distal sections showed a definite sparsity of the elements of the plexus as contrasted with those sections more proximal. A block from the descending colon showed only a rare ganglion containing an average number of nerve cells, a few supporting cells and almost no nerve fibers. The nerve cells were small and shrunken even for a child. A block from the transverse colon revealed that the ganglions were normal in number and contained the usual number of nerve cells, which stained somewhat poorly with cresyl violet. The interganglionic fibers were decreased in number. A block from the ascending colon showed no abnormality of the plexus.

Summary—There was an absence of ganglions in the rectum, with an apparent gradual transition toward a normal plexus occurring in the dilated sigmoid. There was a region of "thinning out" and atrophy of the plexus that reoccurred in the descending colon, with small shrunken nerve cells and few ganglions. The nerve cells and ganglions became normal again in the transverse colon.

CASE 5—A 24 year old man was seen on Jan 17, 1920, because of abdominal distention and constipation, which had increased in severity during the past year. Five days after birth the patient had had diarrhea, but since that time he had been obstipated. As drugs would not cause the bowel to evacuate its contents, enemas were used frequently. He was unable to pass gas without first inserting a tube into the rectum. As far as was known a normal bowel movement had not occurred since the first days of life. During the past year his condition had been worse, pain had been noted in the right upper quadrant of the abdomen and anorexia was present.

Physical examination revealed a man whose height was 5 feet 11 inches (180 cm) and whose weight was 190 pounds (86.2 Kg). The abdomen was markedly distended and tympanitic. The heart was displaced upward to the third interspace as a result of the abdominal distention.

Since the patient failed to respond satisfactorily to medical treatment, a double-barreled ileostomy was performed on January 27. Some soiling of the peritoneum

occurred at the time of operation, and the patient died on the day of operation as a result of peritonitis and bronchopneumonia

Microscopic Study—Blocks taken from the rectum and from two levels of the transitional region showed no ganglions to be present. No nerve fibers were seen with the exception of a small nerve trunk in one section. Two blocks taken from the sigmoid showed only a few ganglions. These contained only one to four nerve cells each. The usual supporting cells and nerve fibers were scarce. Two blocks from the descending colon showed that the ganglions were somewhat diminished in number and contained fewer nerve cells than was usual for this part of the colon. There were definitely more ganglions here than in the sigmoid. Two blocks were taken from the transverse colon, one was similar to those from the sigmoid and the other similar to those from the descending colon. A block taken from the ascending colon showed fewer ganglions and fewer nerve cells than the normal amount. The cecum was similar except that there were even fewer ganglions, only five being seen in a strip 3 cm. in length.

Summary—Ganglions were absent in the rectum and in the transitional segments of the colon. Above this level they were considerably diminished in number as compared to the findings in the cases used as controls.

CASE 6—A 21 year old woman was seen on Aug. 9, 1917, because of distention of the abdomen and obstipation. She had been constipated since early childhood and would go without bowel movements for two weeks at a time unless enemas or a strong physic was administered. When she was constipated, melena was present.

Physical examination revealed a woman with a hugely distended abdomen. Her height was 5 feet 2 inches (157 cm.), her weight was 97 pounds (44.0 Kg.) and her blood pressure was 130 mm. of mercury systolic and 100 diastolic. The abdomen was distended by a huge colon. Visible peristalsis was present and active. Fecal masses were felt in the abdomen. Roentgenographic examination revealed a megacolon.

The patient did not do well and died the day after examination. At necropsy a perforation of the cecum, with gross contamination of the peritoneum by feces, was found. The diaphragmatic apices were at the third ribs bilaterally.

Microscopic Study—Three blocks taken from the rectum and two blocks taken from the lower part of the sigmoid showed no vestige of the plexus of Auerbach. An occasional nerve bundle was seen. A block taken from the upper part of the sigmoid, which was the thickest and most dilated portion, showed a plexus which was normal except for a diminution in the supporting cells and fewer nerve cells per ganglion than were normally encountered. Seven blocks from the descending colon, transverse colon, ascending colon and cecum showed an essentially normal plexus.

Summary—Absence of plexus was noted in the rectum and in the lower part of the sigmoid. There was some diminution of the number of ganglions proximally, but the descending colon and the remainder of the colon showed a plexus that was within normal limits.

CASE 7—A 3 year old boy was seen on Feb. 14, 1917, because of constipation. The patient had been constipated since the age of 6 months. At times two weeks would pass without a bowel movement. An infant brother was said to be similarly affected, and a second cousin had died of a similar condition at the age of 31 years.

On physical examination the abdomen was distended (circumference 40 inches [102 cm]) and tympanic. The rectum was empty.

The pulse and temperature suddenly rose, and the patient died on February 19. An enormously distended and redundant colon was found at necropsy, with maximal involvement noted in the sigmoid.

Microscopic Study—Three blocks from the terminal segment of the colon showed the plexus to be absent. In one block just above this in a transitional region and in seven blocks from the sigmoid, descending colon, transverse colon, ascending colon and cecum the plexus was within normal limits.

Summary—There was an absence of the plexus in the rectum, and there was an abrupt change to an essentially normal plexus in the transitional region of the lower part of the sigmoid colon.

CASE 8—A 4 year old boy was seen because of abdominal distention and obstipation since birth. It was stated that he had never had a normal bowel movement. Enemas and suppositories were used, with only a palliative effect. Drugs were of no value.

The blood pressure was 110 mm of mercury systolic and 80 diastolic. The abdomen was distended. The concentration of hemoglobin was 11.4 Gm per hundred cubic centimeters of blood. Roentgenographic and roentgenoscopic examination showed a megacolon to be present and to involve the entire colon above the rectum. The patient was hospitalized and prepared for operation over an eighteen day period. Resection of the colon from the ascending colon to the sigmoid and subsequently a double-barreled sigmoidocolostomy were performed. The patient returned two months later for closure of the colonic stoma. Subsequent to the closure of the stoma, peritonitis developed owing to perforation of an ulcer of the cecum. The peritonitis led to the death of the patient on the sixth post-operative day.

Microscopic Study—Three blocks taken from different levels of the normal rectum showed an absence of the plexus (fig 7 b). At fairly regular intervals there were nerve fibers somewhat similar to those seen in the normal plexus, but there were no ganglions or nerve cells.

One block from the descending colon showed only a slight reduction of the number of ganglions and nerve cells. The findings in the transverse colon were similar. The ascending colon was within normal limits except for a rather marked reduction of the number of ganglions and nerve cells. The ileum showed a normal plexus.

CASE 9—A 1 year old infant had had no normal bowel movements since birth. A daily enema had been given for several months with good results until recently, when the infant had been unable to expel all the enema and as a result the abdomen remained distended. Vomiting and blood in the stools had been present during the week prior to the time the patient was seen at the clinic.

On examination the child was fretful and pale, with a distended abdomen. The concentration of hemoglobin was 32 per cent of normal. Roentgenographic and roentgenoscopic examination showed the sigmoid to be enormous. The rest of the colon was atonic but would contract. Resection of the descending and sigmoid colon was performed a month later. General peritonitis and death occurred four days after operation.

Microscopic Study—Four blocks of the rectum showed no ganglions or nerve cells. Small nerve bundles were frequently seen in the sections. Seven blocks from the sigmoid and the remainder of the colon showed a normal plexus to be present.

Summary—The plexus was absent in the normal-sized rectum. There was a normal plexus in the remainder of the colon.

CASE 10—An 8 month old male infant was seen because of obstipation since birth. Up to 3 days of age there were no bowel movements, and the infant vomited all his feedings. He was given posterior pituitary injection at this time, with five bowel movements occurring in the following two hours. The bowels moved freely for the next two and a half weeks but since then had not moved unless a cathartic or enema was administered. Fecal impactions had been removed at times.

On examination the infant was seen to have an enormous abdomen, 51 cm in circumference. Visible peristalsis was present. There was no beneficial result after medical treatment, and appendicostomy was performed. Death occurred nine days after operation. The clinician in charge felt that toxemia caused the death. No peritonitis was found at the time of the postmortem examination.

Microscopic Study—Two blocks from the rectum showed that no vestige of the plexus was present. A number of nerve bundles were present in the sections. Two blocks from the sigmoid showed an absence of plexus, and no nerve bundles were noted. The descending colon contained an occasional ganglion with a few nerve fibers and supporting cells. The transverse colon, ascending colon and cecum showed an essentially normal plexus except for the fact that there was a moderate diminution of the number of ganglions and nerve cells.

CASE 11—A 27 year old white man was seen on Nov 20, 1946, because of the diagnosis of Hirschsprung's disease made by his home physician. The patient stated that his bowels never moved normally and that his abdomen had always been large. As cathartics were without effect, he was forced to take colonic irrigations at least once weekly to remove the bowel contents. At the time of the colonic irrigations he would occasionally note a retention in the bowel of as much as 1 to 2 gallons (4 to 8 liters) of enema fluid. Crampy abdominal pain had been noted at times. The diagnosis of Hirschsprung's disease was first made when he was 12 years old, and spinal anesthesia was administered on several occasions "to tone up the nerves of the bowel." This was without benefit.

Physical examination disclosed the height to be 68 inches (173 cm) and the weight 153 pounds (69.4 Kg), the nutritional state seemed good. The blood pressure was 127 mm of mercury systolic and 70 diastolic, the pulse rate 88 beats per minute and the oral temperature 98.2 F. The abdomen was greatly enlarged, and flaring of the lower ribs was present. The descending colon was easily palpated and seemed about 10 cm in diameter. The transverse colon was also palpable. Proctosigmoidoscopic examination revealed the terminal segment of bowel to be normal for a distance of 24 cm. Roentgenoscopic and roentgenographic examination of the colon revealed a normal rectum and lower part of the sigmoid, but the remaining part was notably dilated and elongated proximally from the lower end of the descending colon. Roentgenographic examination of the chest revealed bilateral elevation of the apexes of the diaphragm. The concentration of hemoglobin was 14 Gm per hundred cubic centimeters of blood, erythrocytes numbered 4,200,000 and leukocytes 7,400 per cubic millimeter of blood. Urinalysis gave results which were within normal limits. The flocculation reaction for syphilis was negative. An operation was performed on December 2, at which time the ileum was divided at a point about 8 to 10 inches (20 to 25 cm) from the ileocecal valve, the colon was divided in the region of the first portion of the sigmoid and the intervening colon was removed. The ends of the ileum and sigmoid colon were brought out as an exteriorization procedure.

The examination of the removed colon showed maximal dilatation of the descending portion, which was 20 cm in diameter. There was a normal-sized sigmoid colon, beginning abruptly below the region of maximal dilatation. Proximal to the descending portion there was a gradual diminution of the size until a moderately dilated and hypertrophied cecum was seen. The colon was markedly elongated. The appendix was within normal limits, the ileum was not dilated.

Microscopic Study—Blocks of tissue were taken from two levels of the non-dilated sigmoid. Examination of sections from these blocks showed no ganglions or nerve cells. Nerve trunks were fairly frequent and were large. There was an unusually large amount of connective tissue between the longitudinal and circular muscle coats. This same increase of connective tissue was present in all sections until the distal end of the dilated descending colon was studied microscopically, at which time the connective tissue was found to be not increased. This was the largest and only really significant amount of connective tissue found between the muscle layers of the colon in the 11 cases studied.

Two blocks of tissue were taken from the region of transition of nondilated sigmoid to dilated descending colon. The findings were essentially the same as in the sigmoid except that the nerve trunks were not present in the proximal sections and the connective tissue between the muscle layers was normal in the proximal sections.

Blocks of tissue were taken from four levels of the dilated descending colon. The most distal of these showed several ganglions to be present. These contained two to twelve nerve cells each. This was an abrupt change, as the previous block, 2 cm distant, showed no ganglions. The other blocks from the descending colon showed a few more ganglions than the first, the maximal number being eight in a section 4 cm long (the next most proximal). These were all larger than are seen as a general rule in normal cases and contained a greater than average number of nerve cells. They were present in the longitudinal muscle coat rather than between the longitudinal and circular muscle coats. This was the first time that this location had been occupied consistently by the myenteric plexus. It had been noted at times and in the case of single ganglions had been seen frequently, but at no time had the myenteric plexus been in the longitudinal muscle coat for almost its entire extent. The muscle walls were the thickest that we have examined.

Three blocks were taken from the descending colon. These showed many ganglions, with numerous nerve cells, present in the usual location of the myenteric plexus.

Two blocks were taken from the transverse colon. These showed the ganglions of the distal section to be few and small. Those in the proximal sections were essentially normal.

Blocks taken from the ascending colon and the cecum showed a normal number of ganglions and nerve cells.

STUDY OF THE MYENTERIC PLEXUS IN FIVE CASES OF SECONDARY MEGACOLON

In addition to the series of cases used as controls, we have studied 5 cases of secondary megacolon (table 5). The gross pathologic changes of the colon in the first 3 cases were identical with those seen in cases of congenital megacolon, and the gross changes in the last 2 were likewise similar except for the absence of great hypertrophy. It is not

intended to report these cases in detail but rather to bring out the features which distinguish secondary megacolon from congenital megacolon

CASE 12—A 54 year old man had for two years noted constipation and the frequent urge to defecate. For four months blood had been observed in the stools, which were smaller and more frequent than usual. For two months he had noted distention of the abdomen, which was partly relieved by enemas. Appendicostomy was performed without benefit, and death occurred seven days after operation. Postmortem examination revealed an annular, hard, fixed rectal tumor 2 inches (5 cm) above the prostate. There was grade 3 to 4 dilatation of the colon (on the basis of 1 to 4, in which 1 designates the least and 4 the greatest dilatation) and the walls were 5 to 7 mm thick. Microscopic sections taken from the rectum, rectosigmoidal region, sigmoid colon, transverse colon and cecum showed ganglions of the myenteric plexus in every section. These were considered to be normal.

CASE 13—A 36 year old man had noted cramps, constipation and abdominal distention for the past five years. At the time of postmortem examination a grade 4 dilatation and thickening of the colon was seen to be present proximal to a carcinoma of the upper part of the sigmoid. Microscopic sections taken from regions below and above the tumor showed normal ganglions of the myenteric plexus in every section.

CASE 14—A 25 year old man had noted persistent constipation for three months, and for three weeks there had been involuntary defecation and bleeding from the rectum. He died suddenly the day after registration at the clinic. The entire colon was dilated (grade 3 to 4), with thickening of the wall. There was an annular adenocarcinoma 3 cm proximal to the anus. Microscopic sections taken from the rectum, rectosigmoidal region and the remainder of the colon showed the ganglions of the myenteric plexus to be present in every section.

CASE 15—A 62 year old woman had noted an intermittent watery diarrhea for two years. Ten months before her admission to the hospital she had had an episode of abdominal distention, which had been relieved by enemas. Four days before admission, mild abdominal distention had been noted, and two days afterward a rapid increase of abdominal distention occurred with persistent obstipation. Transverse colostomy was performed, but death occurred six hours after operation. Postmortem examination showed the colon to be distended (grade 4), with a greatly redundant and elongated sigmoid colon and mesentery which had permitted a volvulus of the sigmoid. The wall of the bowel was thickened. Microscopic sections taken from many regions of the rectum, sigmoid and the remainder of the colon showed ganglions of the myenteric plexus to be present in every section.

CASE 16—A 33 year old woman had been well until sixteen hours before her admission to the hospital, when she noted abdominal pain and distention and vomited several times. The colon was hugely dilated, as shown by roentgenographic examination. On the day of admission cecostomy was performed, but death occurred shortly thereafter. The colon was hugely distended and thin. The diameter of the colon was 14 cm, and the length was 170 cm. Severe acute colitis was present, with a pseudomembrane over the mucosal surface. The submucosa, muscle layers and peritoneum revealed microscopic evidence of severe inflammatory changes. Microscopic study of the myenteric plexus showed only a fourth of the usual number of ganglions to be present in the rectum, sigmoid and the descending and transverse colon. The ascending colon contained only a few nerve cells, and

there were no visible nerve cells in the cecum. There was considerable diminution of the number of ganglions in the ileum, but the jejunum showed a normal plexus. The changes in the myenteric plexus differed from those seen in cases of congenital megacolon by the fact that the plexus was absent proximally rather than distally and there was generalized damage to the plexus.

Gross examination in the 3 cases in which the megacolon was secondary to obstructing carcinoma showed great dilatation and hypertrophy of the colon above the obstructing lesion. The myenteric plexus was entirely normal in all 3. In the cases of congenital megacolon there were the same dilatation and hypertrophy of the colon above a bowel of normal diameter, with no obstructing lesion in the lumen, but there was an absence of the myenteric plexus in the wall of the distal portion of the bowel. The changes in the myenteric plexus in case 16 were probably related to the severe and fulminating pseudomembranous colitis, although there was no apparent universal involvement of the myenteric plexus by the inflammatory process.

TABLE 6—*Summation of Authors and Collected Series*

Series	Cases	Plexus Absent in Distal Portion of Colon	
		No	%
Our series	11	11	100
Collected series*	18	14	78
Total	29	25	86

*The 4 cases in the collected series in which changes in the distal part of the colon were not reported may not have been completely studied.

COMMENT

Table 6 shows a compilation of the collected series and our series which represent the cases of megacolon in which studies of the myenteric plexus have been carried out. There was a total of 29 such cases, in 25 of which the myenteric plexus was observed to be absent in the distal portion of the colon. In 4 cases there were changes in the plexus other than absence of the ganglions. Since this group of 29 cases consisted of cases of megacolon without reference to the type, we have separated the cases of congenital megacolon. There were 6 cases of definitely congenital megacolon among the 18 collected cases, but since the case reported by Robertson and Kernohan has been used in our series it will be included only in the group that we studied. We have thus collected from the world literature 5 cases of congenital megacolon in which the myenteric plexus had been studied. We have added 11 cases of our own, making a total of 16 cases. In 100 per cent of these cases there was absence of the ganglions of the myenteric plexus in the distal segment of the colon (fig 5). It is our impression that similar changes can be observed in all cases of congenital megacolon in which the criteria that

we have used are fulfilled. As can be seen from the reported cases, there is absence of the ganglions of the plexus in some cases of acquired megacolon. We consider this as a separate but related problem, and a brief mention of another opinion should be made here in this respect. Etzel²⁰ stated that in all cases of nonobstructive acquired megacolon which he studied there were lesions of the myenteric plexus in the neighborhood of the pelvicorectal sphincter.

We have described a pathologic lesion present in 11 of our own cases and in 5 collected from the literature that represent congenital megacolon of a type defined by us. Hawkins, Alvarez, Hurst and Bockus all have stated that a disturbance of the innervation of the colon is the most likely cause for megacolon. Our findings are indicative not only of a pathologic change in the myenteric plexus and in the colonic innervation but of changes which are present in the distal segment of the colon where an obstructing lesion, either neurogenic or gross, would most likely be of significance. The experimental production of megacolon by Ishikawa, Adamson and Auld and by Kleinschmidt is based on an interference with the innervation of the colon.

It is impossible to deny the presence of the changes in the myenteric plexus in cases of congenital megacolon. Likewise, from the theoretic and experimental standpoint the significance of the changes in the myenteric plexus seems to be all that could be desired to explain the pathogenesis of congenital megacolon. When we reviewed the physiologic studies on the innervation and functional activity of the colon, results of various forms of treatment and effects of denervation on the myenteric plexus, we found a wide and chaotic field of contradictions which we have not attempted to untangle. The field is a difficult one to investigate, and the conclusions that are incontrovertible are few.

The following is a brief review of certain aspects of the subject which summarizes the function of the myenteric plexus, although not from an unassailable viewpoint, as related to the consideration of the pathogenesis of megacolon. The sympathetic nervous system is generally conceded to have an inhibitory action on the colon and thus causes retention of the fecal contents and retards the emptying of the colon. The parasympathetic nervous system has an augmentative action on the colon that causes evacuation of the fecal contents and accelerates the emptying of the colon. The internal anal sphincter will relax after parasympathetic stimuli and undergo an increase in tone after sympathetic stimuli.²¹ With such a physiologic basis, it has been postulated that the cause of

20 Etzel, E. Personal communication to the authors.

21 Best, C. H., and Taylor, N. B. *The Physiological Basis of Medical Practice*. A University of Toronto Text in Applied Physiology, ed. 4, Baltimore, Williams & Wilkins Company, 1945, p. 501. Hurst.^a

the fecal retention in cases of megacolon is an overactivity of the sympathetic nervous system in the presence of a normally active parasympathetic nervous system. The tendency generally, however, has been acceptance of the hypothesis that there is a diminished activity of the parasympathetic nervous system, which has a causative effect in the production of megacolon, aided also by the postulated presence of a relative increase in the action of the sympathetic nervous system. A lesion of the autonomic nerves to the colon or of the myenteric plexus or both would be expected to be present if a pathologic lesion were the cause of the autonomic unbalance.

We have found no studies of the nerves leading to the colon in cases of congenital megacolon and have been unable to carry out such a study with the specimens available. Etzel²² studied the vagus nerves in cases of megaesophagus and found them to be normal although he demonstrated changes in the myenteric plexus of the esophagus similar to those that he found in cases of acquired megacolon. Hence we have only minor inferential evidence in regard to the absence of a lesion of the autonomic nerves leading to the colon.

The myenteric plexus and other nervous plexuses of the gastrointestinal tract have been studied in laboratory animals,²² and most of the reported studies have been made on the esophagus, stomach and small bowel rather than on the colon. Therefore there have been relatively few reports in the literature that have a direct bearing on the problem of the myenteric plexus in the colon of man. According to the studies on animals, the plexus in the colon basically consists of nerve cells collected in groups or ganglions which are connected by non-myelinated nerve fibers of extrinsic and intrinsic derivation. A large percentage of the nerve fibers in the wall of the colon come from the extrinsic nerves and disappear after degenerative section of these nerves.²³ Hill's^{15a} impression was that nearly all the sympathetic fibers in the colon are postganglionic and end on the muscles of the colon. She also described most of the parasympathetic fibers as preganglionic and ending in relation to the nerve cells of the myenteric plexus. There would thus be an absence of parasympathetic impulses to a segment of colon that exhibited an absence of the myenteric plexus. A possible physiologic correlation has thus been added to the theoretic, experimental and pathologic aspects of the pathogenesis of congenital megacolon.

22 Footnote 15 Babkin¹⁸

23 Alvarez, p 192 Modern and Thienes^{15d} Johnson^{1e}

SUMMARY

1 The myenteric plexus has been studied in 11 cases of congenital megacolon, a series of cases used as controls and 5 cases of secondary megacolon

2 The myenteric plexus was found to be absent in the most distal part of the colon in all cases of congenital megacolon. In 80 per cent of the cases it was absent also in the "transitional region." In 60 per cent of the cases it was in addition absent in the lower part of the sigmoid. In 20 per cent of the cases the absence of the myenteric plexus extended from the rectum into the upper part of the sigmoid and the descending colon.

3 In all cases of congenital megacolon there were nerves present in the location of the myenteric plexus which were not seen in the control cases.

4 The strategic location of the changes and a review of previous theoretic concepts, experimental studies and certain physiologic and anatomic studies point toward the significance of processes in the myenteric plexus in the pathogenesis of congenital megacolon.

News And Comment

GENERAL NEWS

Urology Award — The American Urological Association offers an annual award of \$1,000 (first prize \$500, second prize \$300 and third prize \$200) for essays on the result of some clinical or laboratory research in urology. Competition shall be limited to urologists who have been in specific practice for not more than five years and to residents in urology in recognized hospitals.

The first prize essay will appear on the program of the forthcoming meeting of the American Urological Association, to be held at the Biltmore Hotel in Los Angeles, May 16 to 19, 1949.

For full particulars write to the secretary, Dr. Thomas D. Moore, 899 Madison Avenue, Memphis 3, Tenn. Essays must be in his hands before Feb. 15, 1949.

Book Reviews

Hospital Care in the United States By the Commission of Hospital Care
Price, \$4.50 Pp 631 New York The Commonwealth Fund, 1947

This royal octavo volume of 630 pages embodies the studies of hospital care in the United States made by the Commission sponsored by the Commonwealth Fund. The obviously correct assumption having been made that hospital care in the United States is inadequate, a huge amount of factual material is assembled in support of this position. Along with this, elaborate recommendations are made, and these are stated in section II in the form of 181 classified propositions. The reviewer is a little uncertain about the categorical way in which some of these propositions are set down. Being himself neither a sociologist nor a statistician but a teacher of medicine, he has scanned closely propositions 50 to 55, which concern medical education. He feels that these propositions at least are somewhat inadequate from the standpoint of the relation of medical education to hospital service. Indeed, in discussions of this sort it must be clearly realized that the university teaching hospital serves a purpose so entirely different from that of nonteaching hospitals devoted mainly to patient service that the two can hardly be discussed at all under the same heading. It would also have been interesting to have a fuller discussion of the impact of the specialty boards on hospital staffs.

The book is far too comprehensive, however, for a brief review. As a storehouse of factual information it is certainly invaluable, and most of the recommendations are sound and constructive or at least serve as a good starting point for further discussion. This study is beyond question a necessary and outstanding contribution to progress in the field, and its sponsors are to be warmly congratulated.

The Practical Nurse By Dorothy Deming, R.N. Price \$3 Pp 357 New York The Commonwealth Fund, 1947

The Commonwealth Fund has again sponsored a most important book. Recent years have clearly shown that the problems of nursing service cannot be adequately handled by the available supply of trained nurses. Hence, the development of practical nurses to supplement the work done by highly trained experts becomes an obvious need. Mrs. Deming's comprehensive study covers the problem of the practical nurse from every standpoint—historical, educational and economic. It is a book which will be essential to all dealing with problems of nursing service as well as a landmark in the philosophy of nursing education.

Practical Office Gynecology By Karl John Karnaky, M.D. Price, \$7.50 Pp 261, with 238 illustrations Springfield, Ill. Charles C. Thomas, Publisher, 1947

This book does not deal with major operative procedures, but the subject of "office gynecology" is covered in a thorough manner. Anatomy, physiology, endocrine problems, infections and other related topics are all dealt with. There are many excellent charts and tables, and the numerous colored plates are a striking feature. There is an index and a bibliography.

ACUTE DIFFUSE INTERSTITIAL FIBROSIS OF THE LUNGS

Report of a Case

BENJAMIN P. POTTER, M.D.

AND

ISADORE E. GERBER, M.D.

JERSEY CITY, N. J.

FROM TIME to time both clinicians and pathologists encounter cases of diffuse pulmonary fibrosis of undetermined origin. Generally, these cases are characterized by a protracted clinical course without distinctive features. The postmortem examination usually reveals a non-specific chronic inflammatory process with extensive organization of the alveolar structures. In decided contrast to these, Hamman and Rich¹ described a group of 4 cases of pulmonary fibrosis in which both the symptoms and the anatomic findings were distinctive. The disease was usually of comparatively short duration, and the outstanding symptoms were those of weakness, increasing dyspnea, cyanosis and finally death in respiratory failure or failure of the right side of the heart. Even more striking than the clinical picture were the unusual anatomic findings. The lungs showed a diffuse, progressive proliferation of the alveolar connective tissue of a type not previously encountered either by them or by other observers.

The comparative rarity of such instances has no doubt contributed to the delay in their recognition. Hamman and Rich encountered 3 cases within the years 1931 to 1933, but almost ten years elapsed before a fourth case came to their attention. The detailed description of their experiences permitted Eder, Hawn and Thorn² to identify a puzzling case of theirs as belonging to the same group. Likewise, we found it comparatively easy to classify our case once we had become familiar with the reports of the previous authors.

From the Clinical and Laboratory Service of the B. S. Pollak Hospital for Chest Diseases, Medical Center.

1 Hamman, L., and Rich, A. R. Acute Diffuse Interstitial Fibrosis of the Lungs, *Bull. Johns Hopkins Hosp.* 74: 177-212, 1944.

2 Eder, H., Hawn, C. V., and Thorn, G. Report of a Case of Acute Interstitial Fibrosis of the Lungs, *Bull. Johns Hopkins Hosp.* 76: 163-171, 1945.

REPORT OF A CASE

The patient, a 33 year old white male printer, was in good health until April 1945. At that time he noticed that he tired easily and that he was gradually losing weight. Several months later cough, dyspnea and palpitation on exertion and easy fatigability developed, which required rest in bed from time to time. By October his dyspnea had become so severe that he was forced to give up working and was confined to bed almost constantly. At this time a roentgenogram of the chest (fig 1A) showed a normal heart shadow and a peculiar haziness of the lower third of both pulmonary fields, somewhat more marked on the left. The electrocardiogram revealed sinus tachycardia. The internist who saw the patient was puzzled by the case but advanced the probable diagnosis of heart failure and sug-

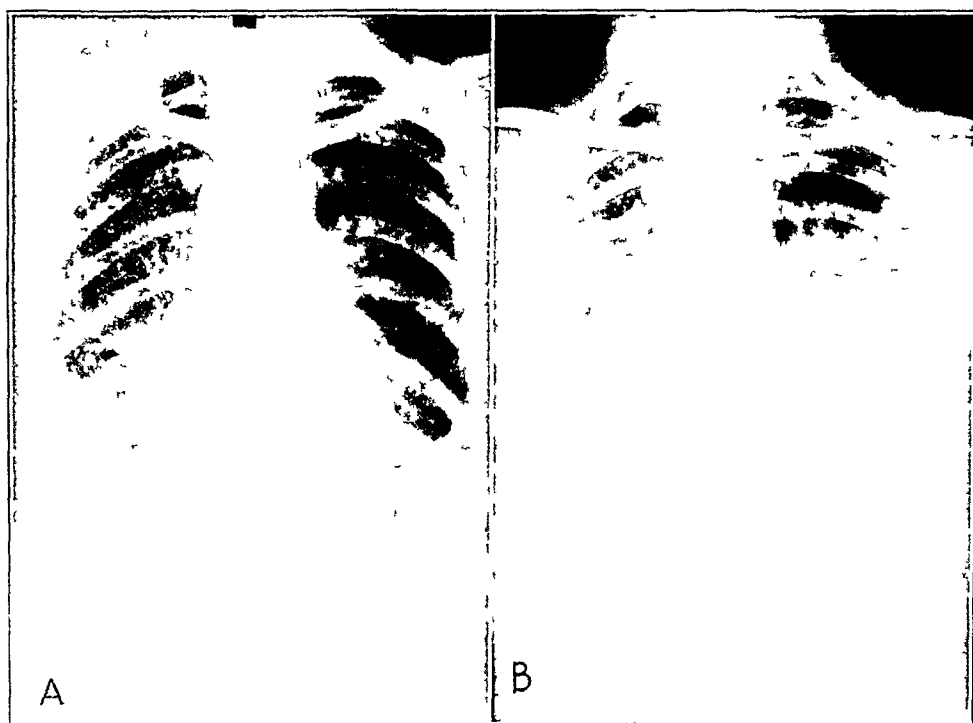


Fig 1—A, accentuation and increase of the pulmonary markings in both lungs, particularly those radiating into the lower lobes. In the latter there is a fine infiltrate most marked in the pericardiac regions. B, roentgenogram taken on the patient's admission to the hospital. Note increase in infiltration and extension into the midpulmonary fields. The infiltrate was so fine that it gave a "veiled" appearance to the lungs.

gested digitalization and diuretics. On November 7 he was seen in consultation by one of us (B P P) because of the confusing clinical picture and the failure to respond to treatment. Hospitalization for further study was advised, and the patient was admitted to the Jersey City Medical Center on Nov 9, 1945.

On admission to the hospital the physical examination revealed evidence of loss of weight, moderate dyspnea at rest, cyanosis and a rasping, essentially non-productive cough. The heart sounds were rapid and regular. A soft systolic murmur was audible over the pulmonic area. There was no evidence of cardiac enlargement. The blood pressure was 119 systolic and 80 diastolic. The findings

in the lungs were remarkably few. There were scattered subcrepitant, inspiratory rales over the lungs anteriorly which disappeared on coughing. The liver was not enlarged. There was no edema of the extremities. Clubbing was not present. The temperature was elevated to 100.2 F. The roentgenogram on admission (fig 1B) showed an extension of the process previously observed. The laboratory findings were all within normal limits. On November 30 the patient was transferred to our care at the Berthold S. Pollak Hospital for Chest Diseases.

Reexamination at this time indicated an extension of the disease as manifested by the notable dyspnea at rest and the increasing cyanosis requiring oxygen by mask intermittently. The examination of the lungs now revealed diminished percussion and moist rales over the lower half laterally and posteriorly. The blood pressure was 90 systolic and 48 diastolic. Repeated roentgenograms (fig 2A) showed little change in the disease process in the lungs. The results of routine

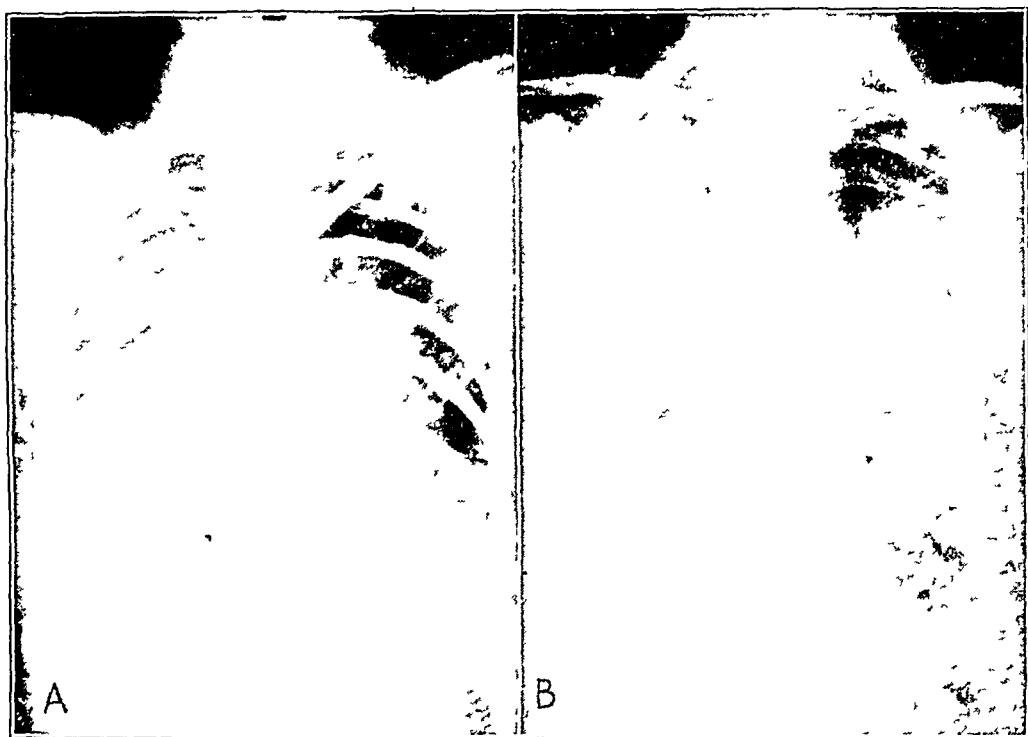


Fig 2—A, taken three days before the sudden rise in temperature from 100.2 to 104.0 F and demonstrating the lack of change since the patient's admission. B, taken when the temperature rose to 104.0 F. The decided increase and extension of the process, sparing only part of the upper lobe of the left lung, are demonstrated.

laboratory examinations were within normal limits. The blood count revealed a hemoglobin content of 95 per cent (Sahli), 4,800,000 erythrocytes and 8,200 leukocytes, with a normal differential count. The chemical examination of the blood showed a nonprotein nitrogen content of 29.7 mg per hundred cubic centimeters, a glucose content of 110 mg and a total protein level of 7.1 mg, of which 4.8 mg was albumin and 2.3 mg globulin. The blood culture was sterile. The urine was normal. The reactions to Wassermann and Kahn tests were negative. Repeated examinations of the sputum and culture and bacteriologic study of the gastric washings did not reveal tubercle bacilli or fungi. The reaction to the tuberculin test was positive in a dilution of 1:100,000 (old tuberculin).

Penicillin aerosol therapy was tried and had to be discontinued when dyspnea and tachypnea required the patient to remain in an oxygen tent continuously. The cough could not be controlled by the usual sedative drugs. The temperature, which hovered around 100.2 F, suddenly rose on December 20 to 104.0 F. At this time roentgenologic examination (fig 2B) showed considerable extension of the hazy appearance in the lungs on both sides so that only the apexes were relatively clear. Parenteral administration of 50,000 units of penicillin every three hours did not affect the fever. Several days later another roentgenogram (fig 3) revealed complete involvement of both pulmonary fields. Tachycardia was marked at this time and was not influenced by digitalis. The patient died on December 26 with pronounced dyspnea and extreme cyanosis. Death was attributed to pulmonary insufficiency.



Fig 3—Involvement of both lungs just before death

Anatomic Findings—At autopsy the striking cyanosis noted clinically was observed. The essential gross abnormalities were limited to the heart and lungs, the remaining organs, aside from considerable cyanosis, were normal.

Heart The organ weighed 300 Gm. The pericardium was smooth. The right auricle and ventricle were markedly hypertrophied and dilated. The left ventricle was of normal thickness and only slightly dilated. The myocardium of both ventricles was firm, no scars or other gross abnormalities were noted. The valves, endocardium and coronary arteries were normal. The great vessels were not unusual.

Lungs The organs together weighed 1,940 Gm. They stood up well. The pleurae were smooth. No fluid was present in either hemithorax. On palpation the lungs were firm and for the most part solid and rubbery except for small areas

which were hypocreptant. On section, an accentuation of the lobular markings was apparent throughout, together with a fine lacelike appearance (fig 4). The cut surface was grayish red and smooth, with but small scattered areas of granular appearance. A mild degree of anthracotic stippling was seen throughout. On close inspection of the hypocreptant areas, outlines of alveoli could be seen. The essentially smooth character of the cut surface was uniform in both lungs from apex to base. The trachea and the main and branch bronchi were patent, and their mucosae were slightly congested. Occasional branch bronchi contained a small

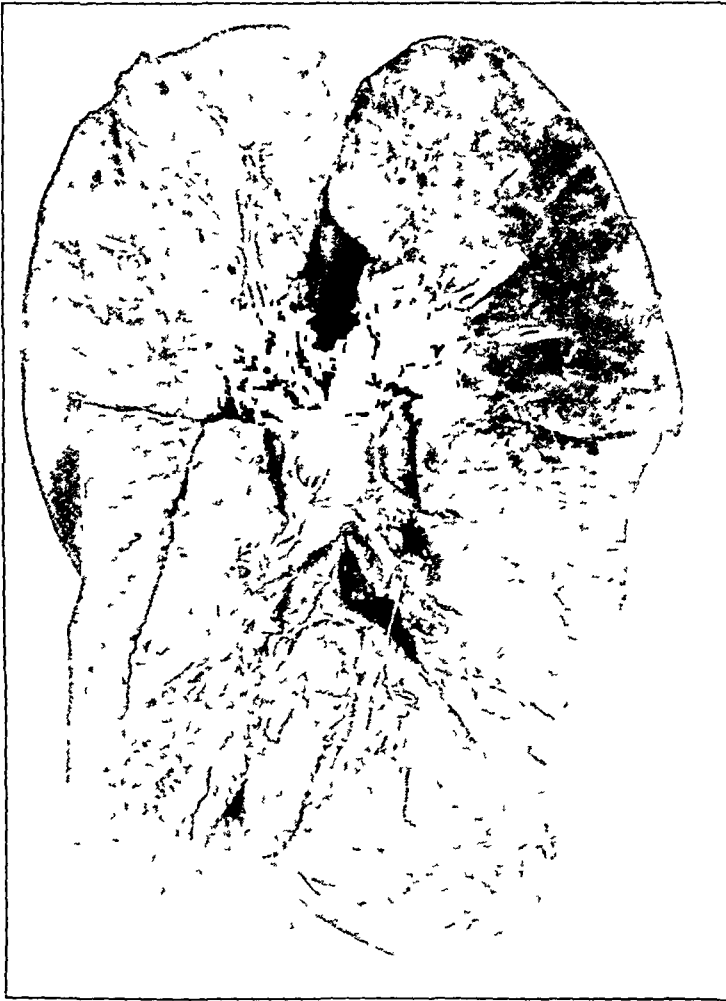


Fig 4—Cross section of the lungs. Note accentuation of all markings and smooth appearance.

amount of thick mucoid exudate. The tracheobronchial lymph nodes were small, soft and moderately anthracotic. The pulmonary arteries and veins were grossly normal.

Histologic examination of the lung revealed a picture that was fairly uniform in multiple sections from all lobes. The predominant feature was the pronounced thickening of the alveolar septums (figs 5 and 6). The thickening was due to varying degrees of connective tissue proliferation. In addition, occasional alveolar septums were infiltrated with polymorphonuclear leukocytes and mononuclear cells.

At times edema of the alveolar walls was also present. The alveolar capillaries were widely dilated and congested. A second striking feature was the presence of a striking proliferation of alveolar epithelial cells, in some instances filling the entire lumen (fig 7) or lining the walls in single layers, imparting a glandular appearance to the alveoli (fig 8). Occasional epithelial giant cells were seen

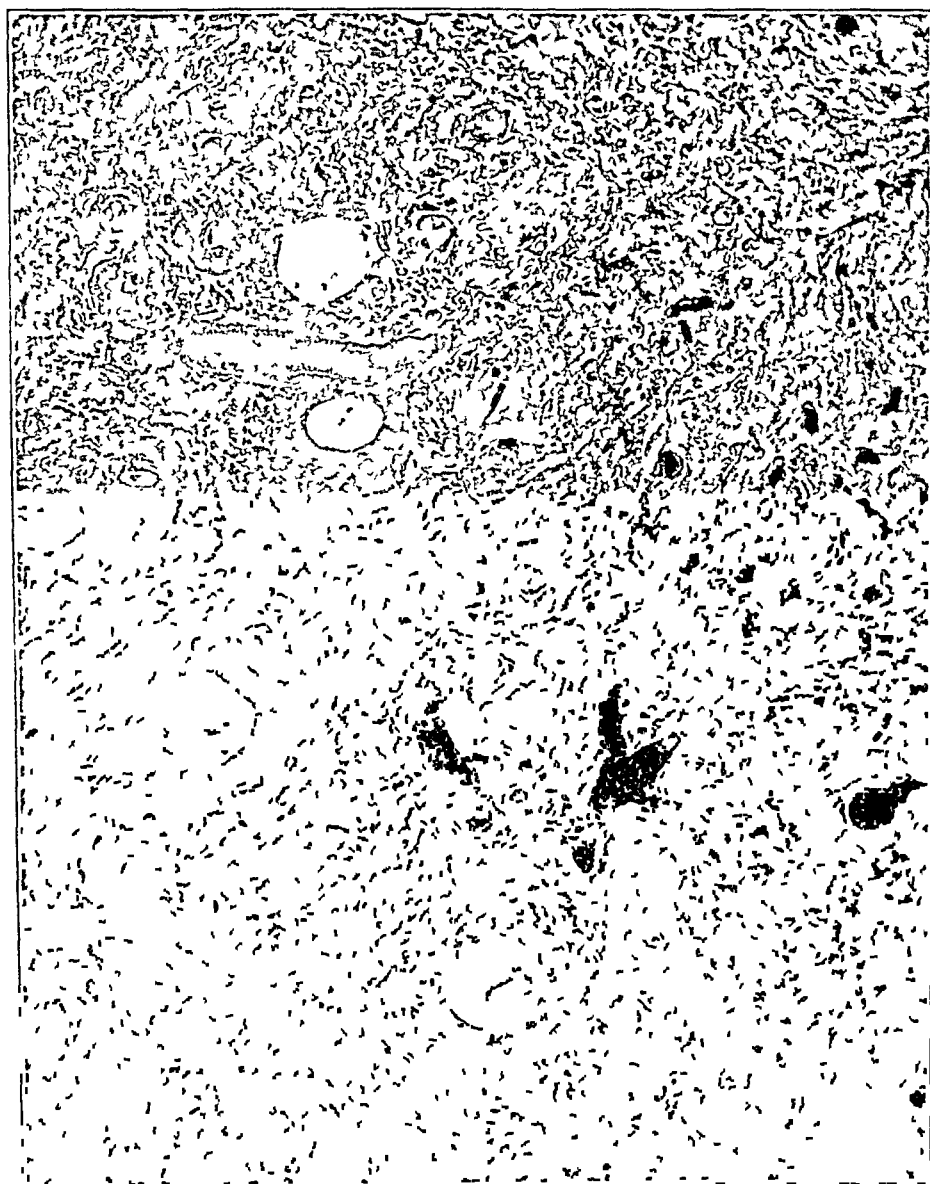


Fig 5—Diffuse character of the interstitial fibrosis in the lungs. Note the pronounced vascular congestion, low power magnification.

Scattered alveoli contained fibrin, and several showed connective tissue organization of the fibrinous exudate. Other alveoli were lined by a broad hyaline membrane (fig 9). Many scattered alveoli contained vacuolated, mononuclear macrophages. Only a few small areas were present in which complete connective tissue organiza-

tion of the alveolar lumens had occurred, as commonly seen in chronic, organizing pneumonitis. The lobular septums were widened by connective tissue proliferation and edema. The bronchioles in some areas contained desquamated epithelial cells.



Fig 6—Pronounced connective tissue proliferation in the lungs, with notable widening of alveolar walls, medium power magnification

and small amounts of exudate composed principally of degenerated polymorphonuclear leukocytes. Occasional bronchioles showed proliferation of the lining epithelium which at times assumed a transitional character, and in a rare bronchiole con-

nective tissue organization of the lumen was seen. The blood vessels were without significant alterations. Only occasional arteries showed elastica proliferation and reduplication of the elastica. Gram and Ziehl-Neelsen stains failed to reveal the presence of bacteria or fungi. Giemsa's stain did not show the presence of inclusion bodies in the epithelial cells.

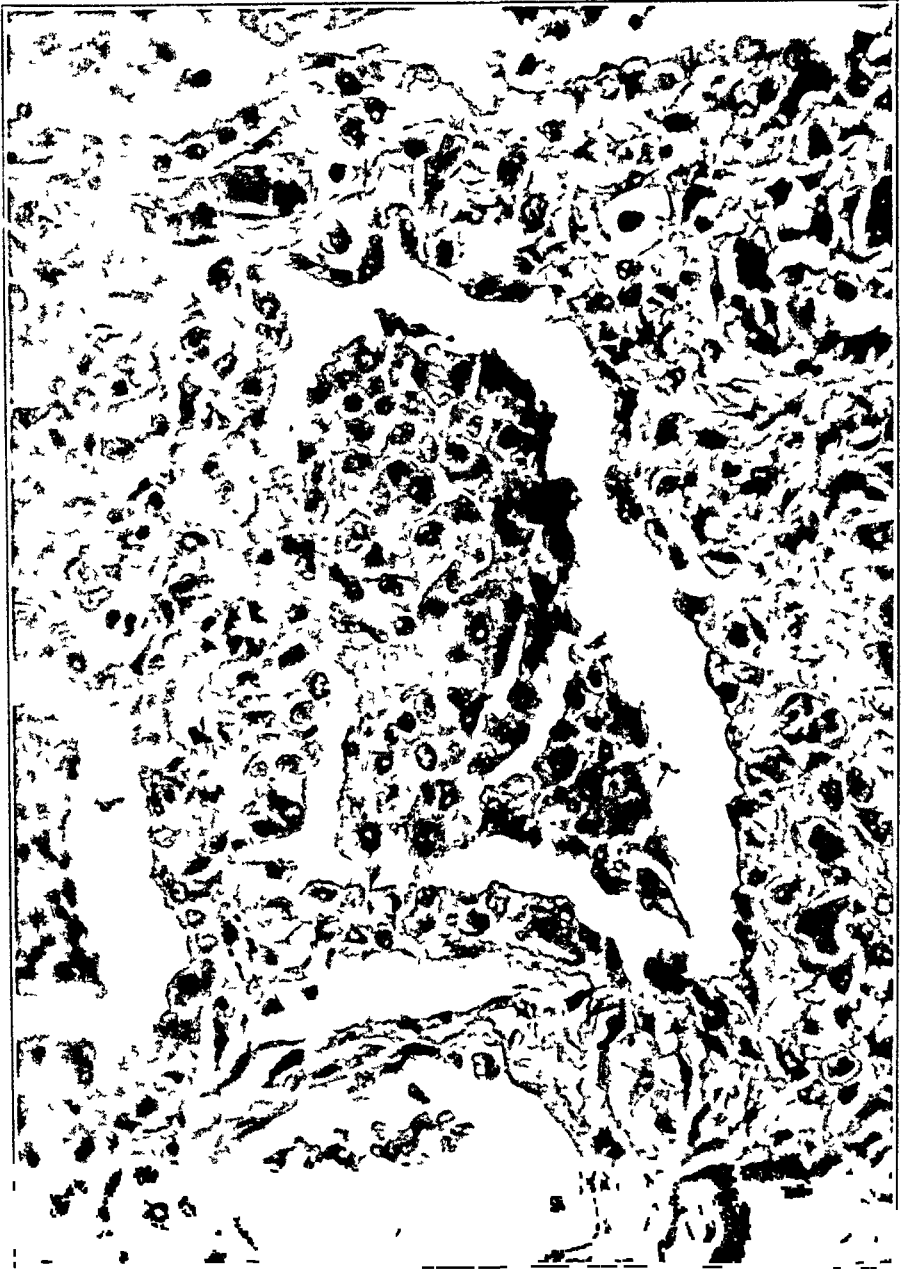


Fig 7—Alveolus in the lung containing a sheet of proliferated epithelial cells. Alveolar walls thickened by fibrous tissue growth, high power magnification.

The tracheobronchial lymph nodes showed only a moderate hyperplasia of the sinus endothelium and secondary follicles.

Other Organs. Results of microscopic examination of the remaining organs were not significant.

COMMENT

The clinical and anatomic findings in our case are in conformity in nearly all respects with those reported by the previous observers. These characteristic features permit ready identification of the cases despite their apparent rarity and support the contention of Hamman and Rich



Fig 8—Alveolar walls in the lung thickened by early connective tissue proliferation and edema. Note proliferation of alveolar epithelium imparting pseudogland appearance to alveoli, high power magnification

that they represent a distinct entity. The lungs and the microscopic sections were shown to Dr. Paul Klemperer at the Mount Sinai Hospital, New York city. He stated that he had never observed a case of this type and was readily able to identify it from the description in the

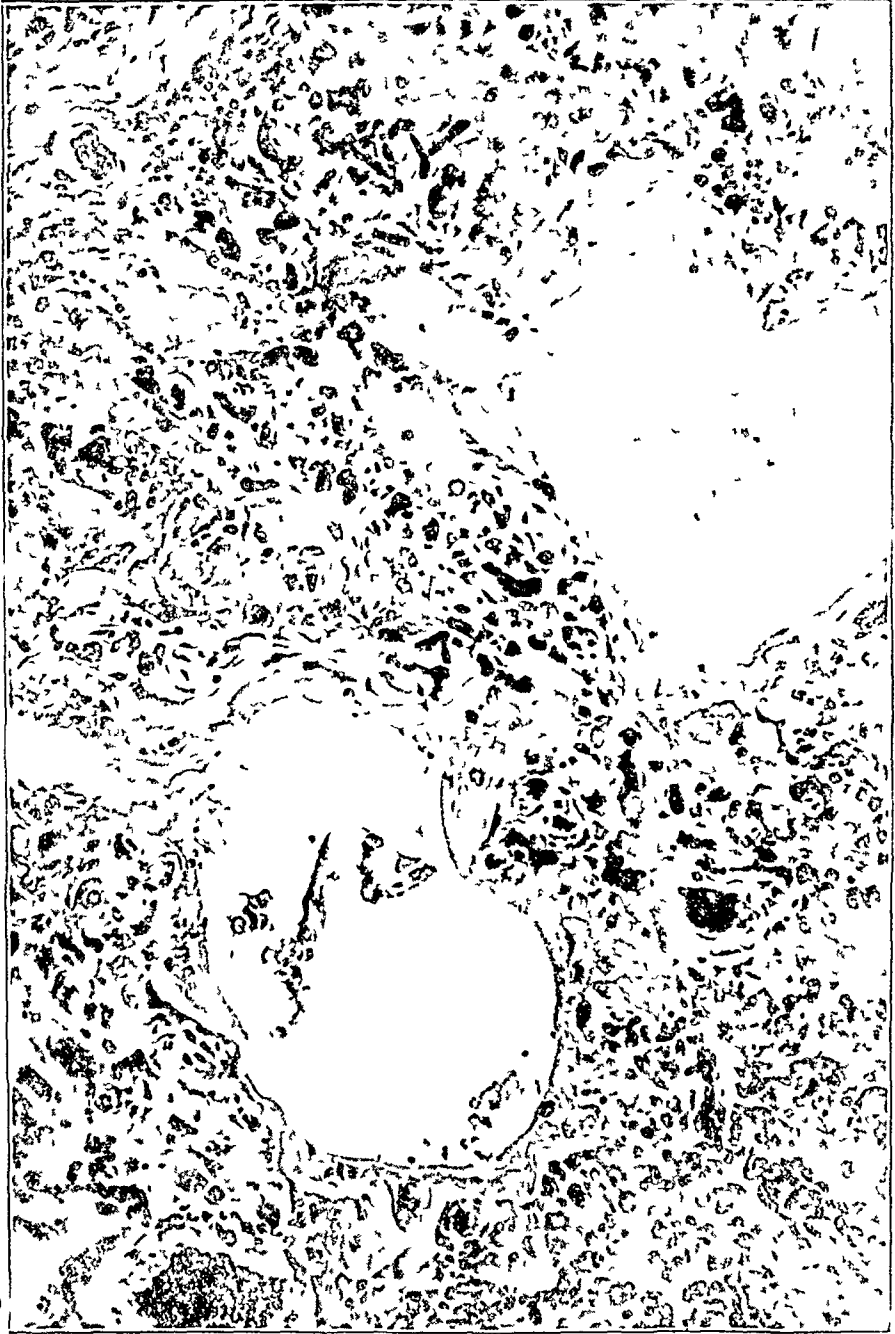


Fig. 9.—Alveolar lumens lined by hyaline membrane in the lung, medium power magnification.

publication of Hamman and Rich. The slides and the roentgenograms of the chest were also seen by Dr. Arnold Rich, who confirmed the diagnosis.

The origin of the clinical symptoms of progressive increase in dyspnea and cyanosis is readily understood in the light of the specific anatomic alterations in the alveolar walls. When these changes are far advanced and universal, as observed in the present case, lack of oxygen is severe and death in pulmonary insufficiency results. As might have been anticipated, an occasional instance of pulmonary osteoarthropathy is noted. This was described in the case of Eder, Hawn and Thorn.

Although in every case thus far reported there was advanced hypertrophy of the right side of the heart, in only 1 was failure sufficiently advanced to produce death. Apparently a fairly marked degree of hypertrophy of the right side of the heart may develop before frank cardiac failure is noted. This may be accounted for by the relatively short duration of the disease, pulmonary insufficiency hastens death before cardiac failure develops. Somewhat similar experiences have been described in cases of lymphangitic carcinosis of the lungs with obstruction to the pulmonary circulation.

The paucity of pulmonary signs on physical examination is striking in view of the subsequent anatomic findings. However, this may be explained by the fact that the lesion is predominantly interstitial in location. A fairly constant finding is that of harsh breath sounds. The presence of crackling and moist rales, together with intensified or distant breath sounds, may be due to the focal bronchopneumonia present in some instances in association with the interstitial fibrosis. The disparity between the physical findings and the roentgenographic appearance is not surprising since similar features have been noted in so-called atypical or virus pneumonia, a disease in which the anatomic lesion is also predominantly in the interstitial tissue, usually about the bronchi.

The gross appearance of the lungs is rather distinctive. The first impression gained is that the underlying process is that of an organizing pneumonitis. However, the fine, interlacing appearance of the section is unlike that usually seen in this condition. The histologic picture is characteristic. In the present instance the features are much like those described by Hamman and Rich in their second case, with the exception that we observed a striking proliferation of the alveolar epithelium. Since somewhat similar alveolar epithelial proliferation has been observed in cases of pneumonia associated with measles and whooping cough, Giemsa stains were made and searched carefully for the presence of cytoplasmic or intranuclear inclusion bodies, none was found. Our patient was exposed to various chemical compounds in the course of his work. These chemicals were obtained and subjected to careful toxic-

cologic analysis. However, nothing was found that could account for the changes in the lungs. As did the other authors, we have concluded that the cause is unknown. Any suggestions as to the cause at the present time would be purely speculative.

The course is rapid and fairly acute. The patients previously described were ill from periods varying from four to twenty-four weeks. As near as could be determined, our patient was ill for a total period of thirty-two weeks. While it is perhaps stretching the term "acute" a little too far to apply it to a disease with a course as long as thirty-two weeks, it would serve no purpose to replace it with the term "subacute." We prefer to retain the title originally introduced by Hamman and Rich so that others may become familiar with the reports in the literature and thereby perhaps aid in facilitating recognition of these cases.

SUMMARY

- 1 The term acute diffuse interstitial fibrosis of the lungs was introduced by Hamman and Rich to describe a comparatively rare group of cases characterized by an acute clinical course and terminating fatally.

- 2 The predominating symptoms are those of progressive dyspnea, cyanosis and a harassing nonproductive cough, with death in respiratory failure or in failure of the right side of the heart.

- 3 The pathologic features are those of diffuse fibrosis of the alveolar walls, with little involvement of the alveolar lumens.

- 4 The present report represents the third in the literature, a total of 6 cases have been described to date.

CLINICAL EXPERIENCE WITH NITROGEN MUSTARD THERAPY

R GOLDMAN, M D

R O EGERBERG, M D

E R WARE, M D

E R EVANS, M D

AND

B G FISHKIN M D

LOS ANGELES

RECENT reports of results obtained with the use of nitrogen mustard derivatives have aroused much speculation regarding the efficacy of chemotherapy in certain malignant neoplastic diseases. The Veterans Administration Hospital, West Los Angeles, Calif. has been designated as a center for the treatment of tumors. This provided a relatively large number of patients who had leukemias and lymphomas, and it was decided to evaluate the effects of nitrogen mustard therapy on a suitable group.

METHOD AND RESULTS

Method—The routine study included a search for enlarged lymph nodes, examination of the liver and spleen, complete blood count, sternal puncture, roentgenologic study of the chest and biopsy. The patient was then presented to the members of a Tumor Board, who selected the type of therapy to be used in each instance. In those patients for whom the nitrogen mustard treatment was recommended, the bis form of the drug was administered intravenously, 0.1 mg. per kilogram of body weight, on alternate days until four injections had been given. Later it was found to be much more desirable to give the injections daily. The most recent change has been to increase the initial number to six, but the number of subsequent injections has been limited to four. The basic dose of 0.1 mg. per kilogram of body weight was adhered to throughout.

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The technic of administration was as follows. An intravenous infusion of 1 liter of isotonic sodium chloride solution was started. Ten cubic centimeters of isotonic sodium chloride solution was then injected into a bottle containing 10 mg of the nitrogen mustard crystals. The required amount of the solution was then withdrawn in the dose of 1 cc for each 22 pounds (10 Kg) of body weight and injected immediately into the rubber tubing of the running sodium chloride infusion. Immediate injection is essential, since the nitrogen mustard is hydrolyzed and ineffective after a few minutes. Most patients will experience nausea and vomiting at some time after injection of the drug. These symptoms can be controlled most effectively by intravenous administration of "sodium amytal" in sufficient amounts to produce narcosis for the duration of the symptoms, which last for about four to six hours. Most of the patients

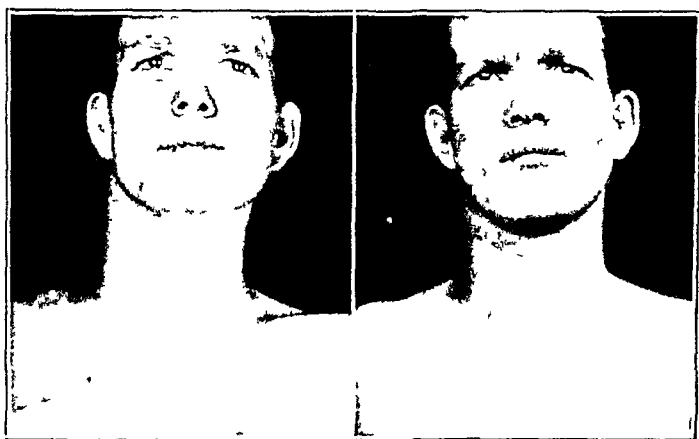


Fig 1 (case 38)—Hodgkin's disease. Patient before and two weeks after the injection of nitrogen mustard.

experienced anorexia for the remainder of the day after injection, it therefore was found practical to administer the drug as late in the day as possible, since the appetite was usually normal by the next morning. Although no quantitative studies were made on this point, it appeared that the patient's strength and weight were better preserved when this plan was used. It was felt that the intravenous infusion of sodium chloride solution, although not necessary, reduced the incidence of thrombophlebitis as well as of nausea and vomiting.

Results—Hodgkin's Disease. Seventeen patients for whom a diagnosis of Hodgkin's granuloma was made were treated. In 15 of these a favorable response was observed at some time after treatment. A summary of the results observed in this group of patients is presented in table 1. Subjective improvement included an increased sense of well-being, a feeling of having greater strength and increased appetite. Objective improvement included decrease in the size of the tumor masses,

TABLE 1—Summary of Results in Hodgkin's Disease

Case	Patient	Age	Date of Onset	Treatment (Dates of First Injections)	Period of Remission	Comments
1	W F C	31	November 1944	Nov 14, 1946 (20 mg)	2 wk	There was slight subjective improvement and objective regression in the size of lymph nodes and spleen. Patient had several subsequent convulsions. Died Dec 18, 1946, no necropsy.
2	W B	40	March 1945	Jan 11, 1947 (30 mg) March 3, 1947 (20 mg) April 14, 1947 (24 mg)	3 wk None None	First course. Subjective improvement and 1/3 reduction in size of spleen and lymph nodes, 5 day remission in fever. Preterminal before last two courses. Died April 19, 1947.
4	K St G	22	August 1946	Dec 28, 1946 (24 mg) Feb 1, 1947 (35 mg)	2 wk 2 wk	Subjective improvement, lymph nodes regressed moderately and transiently. Second course cleared arm edema. Died March 3, 1947.
8	A J M	32	April 1945	Feb 5, 1947 (22 mg) April 1, 1947 (24 mg) June 14, 1947 (35 mg) Sept 28, 1947 (17 mg)	5 wk 8 wk 6 wk	Pronounced subjective improvement and regression in size of lymph nodes, limited regression of spleen. Nodes start recanalizing before symptoms recur.
13	D H K J	29	May 1946	Feb 20, 1947 (30 mg) April 17, 1947 (30 mg) June 16, 1947 (16 mg)	6 wk	Subjective improvement has persisted. Lymph nodes recurred in six weeks. Third course given to intensify effect of treatment before further remission.
15	H N	48	August 1946	Feb 26, 1947 (37 mg) May 17, 1947 (32 mg) July 28, 1947 (32 mg)	6 wk 4 wk	Considerable subjective and objective improvement. The only recurrence has been that of pruritus, which responded to the first two courses but not to the third.
18	A R S	22	February 1947	March 24, 1947 (60 mg) June 14, 1947 (45 mg)	Indefinite Indefinite	No symptoms. Mediastinal mass had regressed to normal and shown no evidence of recurrence. Second course for intensive suppression only.
19	W F S	30	December 1946	April 9, 1947 (30 mg)	Indefinite	No symptoms. Cervical mass regressed with treatment, this was followed by local roentgen ray therapy. No recurrence to date.
22	G W M	32	March 1946	April 16, 1947 (24 mg)	4 wk	Decided subjective and objective response. Treatment was not repeated, and patient died June 22, 1947.
23	M K S	15	1944	May 3, 1947 (24 mg)	None	Patient in preterminal stage when treatment was initiated. No response. Died May 8, 1947.
24	E J	33	December 1946	May 5, 1947 (31 mg) June 19, 1947 (31 mg)	1 wk 4 wk	Considerable subjective and objective improvement. Temperature fell to normal in two days and remained normal for one month. Further treatment withheld because of tendency to marrow aplasia (noted before treatment).
30	G J	59	July 1943	July 1, 1947 (44 mg)	12 wk	Gastric resection in December 1943 showed Hodgkin's infiltration. Nephrectomy March 1947 also showed Hodgkin's disease. Now has pulmonary infiltration. Subjective improvement, with weight gain and slight regression of pulmonary lesion after treatment.
31	J McH	57	August 1946	June 23, 1947 (30 mg) July 22, 1947 (20 mg)	3 wk 3 wk	Patient in preterminal stage, but responded dramatically and was able to sit up after treatment. Visceral Hodgkin's disease without superficial splenomegaly or lymphadenopathy diagnosed on laparotomy and biopsy. Died Sept 29, 1947.
32	LeR B	38	February 1946	June 20, 1947 (15 mg)	None	Patient in preterminal stage when treatment started. Died June 24, 1947.
36	G C	58	May 1945	July 25, 1947 (36 mg)	Indefinite	Subjective and objective improvement. Symptoms still in remission. Also has active pulmonary tuberculosis which was not intensified by nitrogen mustard.
38	A R M	23	January 1946	Aug 1, 1947 (41 mg)	Indefinite	Subjective and objective improvement. While still in remission, roentgen ray therapy was given to the neck, axilla and abdomen.
40	Q N	27	January 1945	Sept 12, 1947 (36 mg)	Indefinite	Subjective and objective improvement. Symptoms still in remission.

lymph nodes and spleen, remission of fever and gain in weight. Four patients (cases 1, 23, 31 and 32) were given their first course of treatment when it was apparent that their disease was preterminal. Three of these died soon thereafter, but 1 (case 31) improved sufficiently to get out of bed and sit up in a chair, he died four months after treatment was initiated. Three other patients died, 2 of these (cases 2 and 4) received definite but transient objective benefit from the nitrogen mustard though they continued their downhill course. The third (case 22) had a satisfactory remission for a month, when it was decided to administer roentgen ray therapy, to which he previously had responded fairly satisfactorily. The irradiation failed to halt the course of the disease at this time, and he died a month later. The photographs in figure 1 demonstrate the decrease in size of a cervical mass two weeks after the initiation

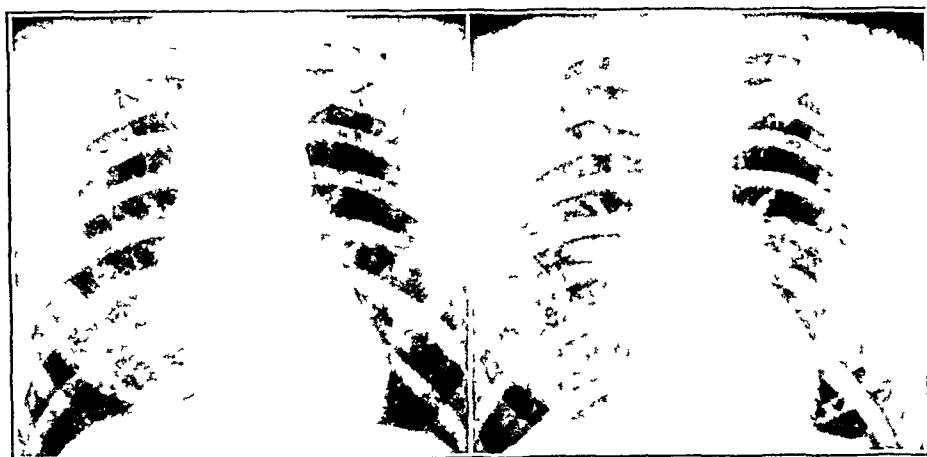


Fig 2 (case 18) —Hodgkin's disease. Regression of a mediastinal mass two months after the initiation of nitrogen mustard therapy. There was further regression in the succeeding two months.

of therapy in a patient (case 38). This patient also had a massive abdominal infiltration which produced intestinal obstruction. This abdominal infiltration regressed, there was a remission of symptoms and there was a reduction in the size of the mass. In figure 2 may be seen roentgenologic evidence of a mediastinal mass before and two months after the initiation of therapy. The patient (case 18) was asymptomatic, and the enlarged mediastinal shadow was found by routine roentgenologic examination. In 1 case (case 15) the major complaint was intractable pruritis. The first two courses controlled this symptom for a period of a month each, but the third course was not effective. One patient (case 36) had Hodgkin's disease complicated by active bilateral pulmonary tuberculosis. A full course of nitrogen mustard therapy effectively controlled the Hodgkin's disease, and there was no evidence that the tuberculosis was affected in any way. The duration of the remissions is difficult

to assess. Patients in the earlier phases of the disease appeared to have suppression of signs and symptoms for about four months, while patients with late disease responded for only a week or two. The average period of remission seems to have been three or four weeks.

Lymphosarcoma and Reticulum Cell Sarcoma Three patients with lymphosarcoma and 3 with reticulum cell sarcoma were treated. Four of these patients were in the preterminal stage when treatment was begun. Only 1 of these (case 5) responded with a transient reduction in the size of the lymph nodes, all 4 died. The condition of another patient (case 28) who had a large abdominal mass was improved. The

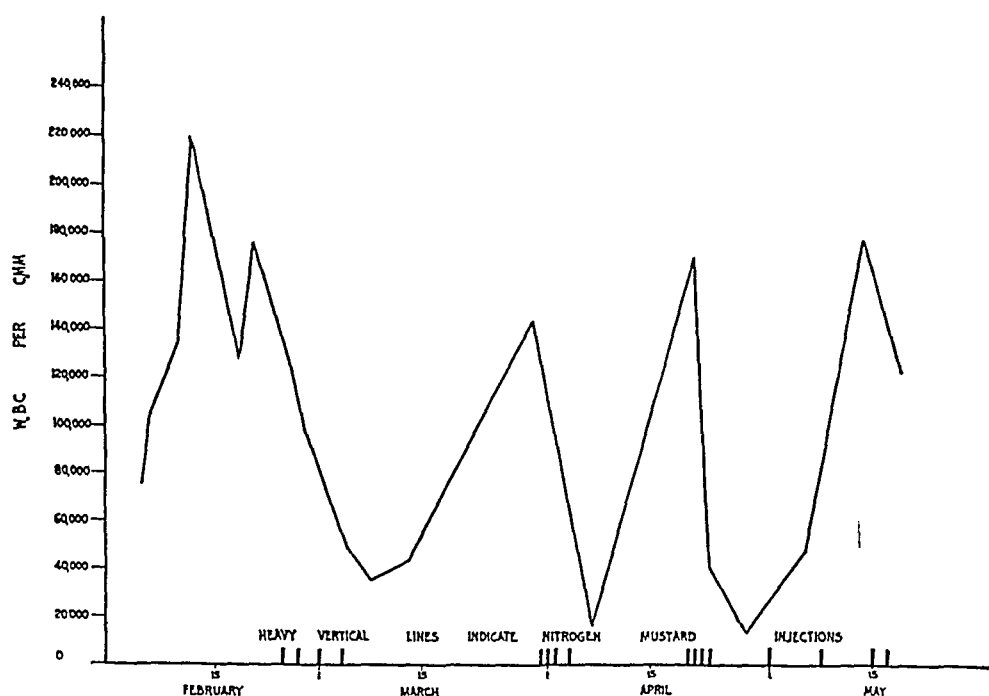


Fig 3 (case 14)—Acute leukemia. Response of white blood cell count to injections of nitrogen mustard.

mass disappeared, and there was a reduction of radicular pain in the back. The mass recurred within two weeks, but the pain continued to be reduced. A second course of therapy was less effective, and the nausea and vomiting were so severe that a third course was refused. One patient (case 33) who had reticulum cell sarcoma responded well, but new nodes appeared three weeks after a course of treatment. Of the 6 patients, 5 are dead. In 3 cases there was some response, in 1 there was no effect on the course of the disease and in 2 there was remission for one to three weeks. The results observed in the patients are summarized in table 2.

Acute Leukemia Five patients who had acute leukemia were treated. All five died. Two failed to respond, 1 demonstrated subjective improvement but no concomitant objective changes. One patient (case 6)

who appeared to be in the preterminal stage stabilized and survived for a period of two and one-half months. A similar patient (case 14), also apparently in the preterminal stage, who had generalized hemorrhages, hypertrophic gingivae, an enlarged spleen and a severe blastic leukocytosis, had a dramatic response, experiencing improvement subjectively and all the favorable objective changes previously described. Figure 3 illustrates his hematologic response. Thus, occasional patients experienced a transient remission after treatment, but the specific response could not be predicted in any case. The results observed in the treatment of these patients are summarized in table 3.



Fig 4 (case 29) —Chronic myelogenous leukemia. Regression of spleen two weeks after nitrogen mustard therapy.

Chronic Leukemia. Two patients who had lymphatic leukemia and 4 who had myelogenous leukemia were treated. In each of the cases of lymphatic leukemia there was a decrease in the leukocyte count after treatment, although the number of cells did not reach levels lower than some observed in the same patients before treatment. One patient (case 7) who had an unsteady gait, slurred speech and difficulty in writing experienced a transient improvement which lasted for a period of two or three weeks, at necropsy leukemia infiltrations were found in the brain stem, and this condition was considered to be an adequate explanation for the signs and symptoms described. Two of the patients with

TABLE 2—Summary of Results in Lymphosarcoma

Case	Patient	Age	Date of Onset	Treatment (Dates of First Injections)	Period of Remission	Comments
5	J W	29	July 1946	Nov 28, 1946 (28 mg)	None	Lymphosarcoma Patient in preterminal stage No subjective improvement but lymph node enlargement decreased Marked aplastic anemia, with a white blood cell count of 150/c mm before therapy Died Dec 7, 1946
12	A A W	50	November 1946	Feb 12, 1947 (26 mg)	None	Reticulum cell sarcoma Patient in preterminal stage No objective or subjective improvement Died Feb 25, 1947
16	C B B	55	April 1946	March 12, 1947 (18 mg)	None	Lymphosarcoma with terminal chronic lymphatic leukemia Patient in preterminal stage No subjective or objective improvement Died March 21, 1947
28	J A H	55	1942	June 3, 1947 (30 mg) June 23, 1947 (30 mg)	2 wk 1 wk	Lymphosarcoma General improvement with relief of nodular pain and intestinal obstruction Abdominal mass 3" in diameter receded but recurred after two weeks Pain did not return with full severity Third course refused Died Aug 10, 1947
33	M F	53	December 1946	July 2, 1947 (41 mg)	3 wk	Reticulum cell sarcoma Subjective and objective improvement, submandibular node decreased from 1½" in diameter until unpalpable Evidence of spinal metastasis and new nodes 3 weeks later
39	W G	51	August 1946	Aug 25, 1947 (36 mg)	None	Reticulum cell sarcoma Some subjective but no objective improvement Patient in preterminal stage Died Sept 20, 1947

TABLE 3—Summary of Results in Acute Leukemia

Case	Patient	Age	Date of Onset	Treatment (Dates of First Injections)	Period of Remission	Comments
6	F B	26	September 1946	Nov 23, 1946 (28 mg)	4 wk	Moderate subjective improvement White blood cell count appeared to have stabilized Patient later received a second course in another hospital, where a spontaneous leg abscess developed Died Feb 25, 1947
9	R M	39	November 1946	Feb 3, 1947 (6 mg)	None	The patient died suddenly on Feb 9, 1947 before the effect of nitrogen mustard was apparent
10	J A P	37	August 1946	Feb 18, 1947 (10 mg) March 12, 1947 (20 mg)	None None	No objective or subjective improvement Nitrogen mustard may have increased thrombopenia and hastened death Died March 21, 1947
14	M D	37	December 1946	Feb 24, 1947 (30 mg) March 31, 1947 (28 mg) April 20, 1947 (30 mg) May 8, 1947 (30 mg)	3 wk 2 wk 2 wk None	Pronounced subjective and objective response, with improvement in gingival hypertrophy, skin hemorrhages and lymphadenopathy Dramatic hematologic response Life probably prolonged about 3 months Patient died May 20, 1947
27	J S	25	February 1947	May 17, 1947 (25 mg) June 9, 1947 (19 mg)	None None	Subjective improvement after first course Morbilliform rash after each course may have been due to nitrogen mustard Death on June 11, 1947 may have been hastened by neutropenia Terminal proctitis

myelogenous leukemia experienced dramatic subjective and objective improvement, there was considerable reduction in the size of the spleen, and there was a fall in the leukocyte count. In 1 case (case 29) the count fell from 107,000 to 5,000 and in the other (case 37) from 150,000 to 12,000. The regression in the size of the spleen in case 29 is indicated in figure 4. Here again, the results were unpredictable. The response in cases of myelogenous leukemia was more favorable than that in cases of lymphatic leukemia. The duration of the remissions was three months. Results observed after the treatment of these patients are summarized in table 4.

Mycosis Fungoides. Two patients for whom a diagnosis of mycosis fungoides was made were treated. The first patient (case 20) responded

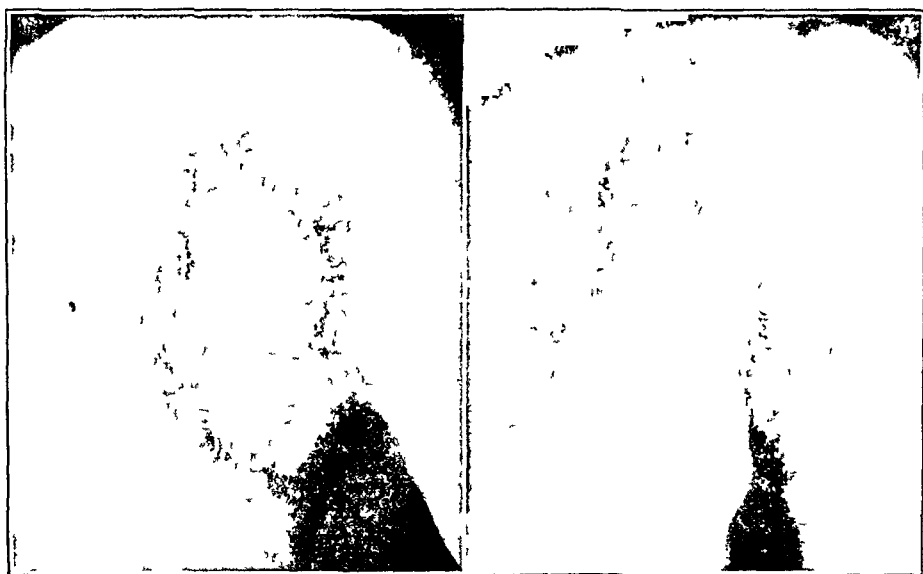


Fig 5 (case 25) —Mycosis fungoides. Before and three weeks after the injection of nitrogen mustard.

satisfactorily after two courses of treatment. There was complete healing of the lesions for the first time within a period of eighteen months. Two weeks after a second course of treatment, a small blister appeared on the heel, the site of the most severe original lesion, and three weeks later this lesion consisted of a tumefaction 3 cm. in diameter and was surrounded by a local inflammatory reaction. This responded only slightly to the third and fourth courses of treatment. The second patient (case 25) also responded satisfactorily. The infiltrated lesions completely regressed, leaving only pigmented scars, the chronic exfoliative dermatitis was diminished, and there was relief from pruritis. The changes which took place may be seen in the photographs in figure 5.

TABLE 4—Summary of Results in Chronic Leukemia

Case	Patient	Age	Date of Onset	Treatment (Dates of First Injections)	Period of Remission	Comments
7	O P S	69	November 1911	Dec 5, 1946 (35 mg)	3 wk	Lymphatic leukemia Transient improvement in gait, speech and writing White blood cell count fell from 26,000 to 9,000 Died March 6, 1947, after exploration of cerebellopontile angle tumor, which was found at necropsy to be a cyst of leukemic infiltrate
11	H R H	52	April 1944	Feb 18, 1917 (12 mg) May 12, 1947 (24 mg)	None None	Lymphatic leukemia Questionable subjective improvement without change in splenomegaly or lymphadenopathy Fall in white blood cell count no greater than normal variation
17	F K	23	December 1915	March 1, 1947 (34 mg)	None	Myelogenous leukemia No apparent subjective or objective response
26	O B M	52	October 1944	May 18, 1917 (26 mg)	None	Myelogenous leukemia Patient preterminally went into a more acute phase of his leukemia and had diarrhea and septic course Died May 22, 1947 before effect of nitrogen mustard could be noted
29	F T	58	August 1915	June 8, 1917 (39 mg)	3 mo	Myelogenous leukemia Dramatic subjective and objective improvement Spleen receded 6 cm White blood cell count fell from 107,000 to 5,000 and was 12,000 two months after treatment Died (of coronary arteriosclerosis and heart failure) Oct 15, 1947
37	H G	57	September 1916	Aug 1, 1947 (36 mg)	9 wk	Myelogenous leukemia and postoperative splenic flexure carcinoma Slight subjective and moderate objective improvement White blood cell count fell from 150,000 to 12,500

After three weeks the pruritis recurred, and after two months there were signs of reactivation in one lesion. A third course of treatment was administered, and the results were satisfactory.

Other Conditions Several miscellaneous conditions were treated. In a patient who had polycythemia vera (case 21) there was no reduction in the erythrocyte count two months after a course of treatment consisting of the administration of 26 mg. At this time symptoms forced the use of phlebotomies, and 6 liters of blood was withdrawn. However, since the size of the spleen was diminished by one third, it is possible that the early fall in the red blood cell count was compensated for by the extrusion of red cells from the spleen. At present, six months after the course of nitrogen mustard and four months after the performance of the phlebotomies, the blood count is still well below its original level.

A patient (case 35) with pulmonary metastasis after orchidectomy for a teratoma of the testis had some symptomatic relief, i.e., increased well-being and reduction in obstructive edema of the leg, which lasted from two to three weeks. Another patient (case 34) with bronchogenic carcinoma reported similar symptomatic results and slight relief from bronchial obstruction. In a young man (case 3) who had chronic cervical reticuloendotheliosis there was a moderate regression in the size of the nodes, which lasted about three weeks, but there was no improvement in subjective symptoms.

Toxic Reactions Toxic reactions were infrequent. In 1 patient a small vesiculation developed on the skin where a drop of the material accidentally fell. A second patient received a small amount of nitrogen mustard into the subcutaneous tissues of the antecubital fossa. The area was infiltrated with isotonic sodium chloride solution, and possibly this controlled the reaction. There was a resulting area of heat and tenderness which restricted the full range of motion. No necrotic reaction occurred, and the patient was then free of symptoms except for a slight paralysis of the ulnar nerve, which has now subsided. A moderately painful thrombophlebitis was noted in only 2 patients. Gastrointestinal symptoms were extremely common. Seventy per cent had vomiting, and 80 per cent had nausea from two to six hours after administration. After repeated courses of treatment, it appeared that the percentage of the patients who had these symptoms was much greater. Anorexia was an almost universal symptom and resulted in some weight loss during the course of treatment. No diarrhea was observed in this group of patients. The hematologic effect appeared to be limited principally to the leukocytes. The erythrocyte count was reduced gradually, which corresponded with the course of the disease rather than with the effect of the drug. The effect on the erythrocyte count was also obscured by frequent transfusions which were given to the patients. There was a definite numerical

decrease of leukocytes in all patients treated. The usual range of counts after treatment was 1,000 to 3,500, and this level was reached on about the tenth to the fourteenth day after the initiation of treatment. Return to normal levels generally occurred in the third or fourth week. Large areas of spontaneous suppuration developed in 2 cases. In a patient (case 2) who had acute aleukemic lymphatic leukemia an abscess developed in the right thigh. The leukocyte count dropped to as low a level as 1,500. This level was felt to be due to replacement with blast cells rather than to marrow aplasia. In another patient (case 4), who had Hodgkin's granuloma, large abscesses developed in both buttocks and over one scapula, which when drained yielded a pint or more (500 cc) of pus each. His lowest leukocyte count was 3,600, of which 94 per cent was polymorphonuclear cells. Two patients had cutaneous eruptions which possibly were due to the nitrogen mustard. A patient (case 27)

TABLE 5—*Source of Reported Cases*

September 1946	Goodman and Gilman (New Haven, Conn.).....	7
	Wintrobe and McLennan (Salt Lake City).....	34
	Dameshek (Boston).....	16
	Goodman (Portland, Ore.).....	10
October 1946	Jacobson, Spurr, Barron, Smith, Lushbaugh and Dick (Chicago) ...	59
February 1947	Alpert and Peterson (Washington, D. C.).....	23
April 1947	Henstell and Tober (Los Angeles).....	1
June 1947	ApThomas and Cullumbine (Manchester, England)	25
Total		175

who had an acute lymphoblastic leukemia had a morbilliform rash on the sixth day after initiation of the first course and on the third day after the initiation of the second course of therapy. This rash appeared to be benefited by the use of antihistaminic drugs. However, he had been receiving penicillin as well, and sensitivity to this drug could not be excluded. Copper-colored macules developed in 1 of the patients who had Hodgkin's granuloma (case 31), resembling in character and distribution those of secondary syphilis. No other toxic reactions were noted.

SUMMARY OF PREVIOUS REPORTS

At the outset of this study, the published clinical experience with nitrogen mustard had been summarized in two articles describing its use in the treatment of 126 patients.¹ Later, Alpert and Peterson² reported

1 Goodman, L. S., Wintrobe, M. M., Dameshek, W., and McLennan, M. T. Nitrogen Mustard Therapy, *JAMA* 132:126 (Sept. 21) 1946. Jacobson, L. O., Spurr, O. L., Barron, E. S. G., Smith, T., Lushbaugh, O., and Dick, G. F. Nitrogen Mustard Therapy, *ibid* 132:263 (Oct. 5) 1946.

2 Alpert, L. K., and Peterson, S. S. The Use of Nitrogen Mustard in the Treatment of Lymphomata, *Bull. U. S. Army M. Dept.* 7:187 (Feb.) 1947.

on 23 patients, most of whom had Hodgkin's disease, and Henstell and Tober³ reported its use in a case of mycosis fungoides. Most recently, ApThomas and Cullumbine⁴ reported treatment of 25 patients, bringing the total number of patients treated and reported on to 175. The source of this clinical material is summarized in table 5.

Hodgkin's Disease—Among a group of 90 patients who received treatment for this disease improvement was noted in 84, or 93 per cent. Improvement included partial to complete disappearance of tumor masses, increased appetite, weight, strength and general well-being and absence of fever. The period of remissions varied, in some cases there was none and in others it lasted for eight months. Some patients previously found to be resistant to roentgen ray therapy became sensitive again. No study was made of the effect of the treatment on the ultimate life expectancy after the onset of the disease.

Lymphosarcoma and Reticulum Cell Sarcoma—Twenty-five patients were treated, of which 22 were listed as having lymphosarcoma and 3 as reticulum cell sarcoma. In 14, or 56 per cent, there was indication of some improvement. The remissions were reported to last from two weeks to eighteen months. It was impossible to predict in advance what response might be expected, and several dramatic results were reported for patients in the terminal stage.

Acute Leukemias—Nine patients were treated, and 3, or 33 per cent, experienced some favorable response. The duration of the remission is not given, but from the description of the cases it appears to have been a matter of days at most.

Chronic Leukemias—Fourteen patients who had chronic lymphatic leukemia and 15 who had chronic myelogenous leukemia were treated. Of the group with lymphatic leukemia, 11, or 85 per cent, responded favorably, and of the group with myelogenous leukemia, 6, or 40 per cent, were improved. Again the response could not be predicted in advance. Remissions lasting up to twenty-one months were reported in cases of lymphatic leukemia and up to twelve months in cases of myelogenous leukemia.

Mycosis Fungoides—One case was reported by Henstell and Tober, although 4 more are referred to in an editorial note. In this case there was a dramatic response, with satisfactory clearing of the lesion, but the remission was followed by the authors for only one month. More recently ApThomas and Cullumbine⁴ reported a case in which there was no response.

3 Henstell, H. H., and Tober, J. N. Treatment of Mycosis Fungoides with Nitrogen Mustard, *J. Invest. Dermat.* 8: 163 (April) 1947.

4 ApThomas, M. I. R., and Cullumbine, H. Nitrogen Mustards in Hodgkin's Disease, *Lancet* 1: 899 (June 28) 1947.

Miscellaneous Conditions—The remaining 20 cases fall into several diverse categories. Three patients with giant follicle lymphoma were treated, and all responded with diminution in the size of the lymph nodes although the clinical course continued unaltered. Five patients who had polycythemia vera were treated, and all responded with a remission of three to six months' duration, in 1 case the remission continued for over twelve months. These patients were subjected to phlebotomies often enough to bring the erythrocyte count to normal levels before the nitrogen mustard was administered, and the remission was interpreted as the period during which this count remained normal. Unpredictable relief

TABLE 6—*Comparison of Results with Reported Results*

Diagnosis	Patients Reported on			Wadsworth General Hospital Patients				
	Total	Im- proved	%Im- proved	Total	Im- proved	%Im- proved	Dead	%Dead
Hodgkin's disease	90	84	93	17	15	88	7	41
Lymphosarcoma including reticulum cell sarcoma	25 (3)	14	56	6	3	50	5	83
Acute leukemia	9	3	33	5	2	40	5	100
Myelogenous leukemia	15	6	40	4	2	50	2	50
Lymphatic leukemia	14	11	86	2	1	50	1	50
Mycosis fungoides	2	1	50	2	2	100	0	0
Polycythemia vera	5	5	100	1	1	100	0	0
Miscellaneous (bronchogenic carcinoma, teratoma of testis, chronic reticuloendotheliosis, giant follicle lymphoma, sympathoblastoma, multiple myeloma and others)	15	11	--	3	3	--	1	--
Totals	175	--	--	40	--	--	21	--

of symptoms without concomitant objective improvement was produced frequently in cases of various malignant growths, especially bronchogenic carcinoma.

Toxic Reactions—The most common local reaction appears to have been thrombophlebitis. This was most prevalent after the use of the tris compound and has been much reduced by the use of the bis compound. Nausea and vomiting were universal, and each group had its own method of treatment, no one of which was completely effective. There were concomitant anorexia and loss of weight. However, there was no report of serious diarrhea. The formed elements of the blood were persistently depressed for a period of two to four weeks. No fatal in-

5 Gilman, A., and Philips, F. S. The Biological Actions and Therapeutic Applications of the B-Chloroethyl Amines and Sulfides, *Science* **103** 409 (April 5) 1946. Rhoads, C. P. Nitrogen Mustards in the Treatment of Neoplastic Disease, *J A M A* **131** 656 (June 22) 1946.

fection was reported, in spite of counts as low as 200 leukocytes per cubic millimeter. All patients who survived sufficiently long appeared to have made a satisfactory recovery. No toxic rashes were reported.

COMMENT AND CONCLUSIONS

The theoretic backgrounds of the use of nitrogen mustard have been discussed in considerable detail by other authors,⁵ although even now the exact mechanisms of action are not well known. A complete survey of the clinical results following the treatment of approximately 2,000 patients is to be presented by the Committee on Atypical Growth of the National Research Council. In this report our aim has been to present the results observed in the treatment of a group of patients and to correlate these results with those reports already published.

In general, this group of patients has reacted both qualitatively and quantitatively in close parallel with patients in the reported cases. The greatest discrepancy was that prolonged remissions, reported by others, were not observed by us. The incidence of response in our patients is as close to the reported results as the small size of the group would permit. It is possible that some of the earlier patients in this study might have responded if it had been realized that a significant fall in the leukocyte count was a necessary index of the adequacy of dosage.

Experience has demonstrated that when the drug is given in the recommended dosages the toxic effects are not to be feared. The local reactions of cutaneous vesiculation, extravasation and thrombophlebitis usually can be avoided by care and proper technic. The use of an infusion of sodium chloride solution avoids extravasation and reduces thrombophlebitis to a minimum. Nausea and vomiting can be reduced by adequate sedation and by administration late in the day. The effect on the bone marrow appears to be related to the therapeutic effect, and no patient has failed to recover from leukopenia except when this condition was a part of the primary disease. A total dose of 0.8 to 1.0 mg per kilogram of body weight, given in one course, is reported to be the critical level at which severe and prolonged aplasia is initiated.

Nitrogen mustard appears to offer promise of almost certain remission in Hodgkin's disease and polycythemia vera. Lymphosarcoma, reticulum cell sarcoma, chronic leukemia and mycosis fungoides respond in slightly more than one half of the cases, but such a result cannot be predicted in advance. The response of the other diseases appears to be less consistent, and the group of patients described in this report is too small to permit conclusions of a general nature. The earlier the clinical state of the disease, the more likely is the remission to be clinically significant and the more possible the restoration of the patient to social and

economic usefulness. For diseases in which nitrogen mustard has proved occasionally useful, one course may be tried to determine the patient's response. This should be done for the remission itself and to defer the development of resistance to roentgen rays. Since the first adequate course of nitrogen mustard, judged by the hematopoietic response, appears to be the most effective, failure to respond to the first course obviates the necessity of repeating treatment. Recently, several research groups have begun to study the effects of nitrogen mustard when combined with roentgen ray therapy. It is hoped that this will prolong the duration of the remissions. The rapid response to the drug complements the slower but more prolonged effects of roentgen rays, and this in itself is of value.

SUMMARY

1 Forty male patients who had Hodgkin's disease, lymphosarcoma, leukemia and related diseases were treated with bis-beta-chloro-ethylamine hydrochloride (nitrogen mustard).

2 The results observed in this study are similar, both quantitatively and qualitatively, to those summarized from reports in the literature.

3 Nitrogen mustard appears to be an effective drug in the treatment of Hodgkin's disease, and in some cases of lymphosarcoma, leukemia, mycosis fungoides and polycythemia vera. It appears to offer symptomatic relief in some instances of terminal and metastatic carcinoma of diverse origin.

4 The therapeutic application of the drug results in a prompt response which is more rapid than that which occurs after roentgen ray therapy, but the remission produced is of much shorter duration.

5 No serious toxic reactions were encountered.

6 The theoretic implications of a chemical which can reduce the size of certain tumors or the magnitude of a leukocyte count within a period of a few days, even if the effect is only transient, is of greater significance than the therapeutic applications which have been explored up to the present time.

OSTEOPETROSIS

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OSTEOPETROSIS (Albers-Schonberg's disease) is a rare malady of unknown causation. Little more than 150 cases have been reported in the literature since its discovery in 1904 by a German roentgenologist, Albers-Schonberg.¹ Many names have been used to describe it, notably marble bones,² chalky bones,³ osteopetrosis⁴ and osteosclerosis fragilis generalisata⁵. Some authors have erroneously attributed the earliest description of this disease to Heuck,⁶ who in 1879 described a condition similar to osteopetrosis, now known to be myelofibrosis.⁷ Both diseases present bone marrow fibrosis, hepatosplenomegaly and generalized lymphadenopathy. However, as one can glean from the name, marble bones, the osseous system in this condition is merely abnormally dense, whereas in myelofibrosis one sees a shotty infiltration of the marrow, which may be sclerotic or lytic in nature.

1 Albers-Schonberg, H. (a) Röntgenbilder einer seltenen Knochenerkrankung, München med Wchnschr **51** 365, 1904, (b) Eine bisher nicht beschriebene Allgemeinerkrankung des Skelettes im Röntgenbild, Fortschr a d Geb d Röntgenstrahlen **11** 261-263, 1907

2 Alexander, W G. Report of a Case of So-Called "Marble-Bones," with a Review of the Literature and a Translation of an Article, Am J Roentgenol **10** 280-301, 1923

3 Pirie, A H. The Development of Marble Bones, Am J Roentgenol **24** 147-153, 1930, Marble Bones, *ibid* **30** 618-620, 1933

4 Karshner, R G. Osteopetrosis, Am J Roentgenol **16** 405-419, 1926

5 Davis, G B. Osteosclerosis Fragilis Generalisata, Arch Surg **5** 449-463 (Nov) 1922

6 Heuck, G. Zwei Fälle von Leukämie mit eigenthümlichen Blut- resp Knochenmarksbefund, Virchows Arch f path Anat **78** 475-496, 1879

7 Rosenthal, N, and Erf, L A. Clinical Observations of Osteopetrosis and Myelofibrosis, Arch Int Med **71** 793-813 (June) 1943

Osteopetrosis has no predilection for age or sex, being seen about equally distributed between male and female patients,⁸ the disease has been reported in aged persons⁴ and even in utero⁹ The symptoms are decidedly different in children and in adults, which has led some physicians to consider the condition to exist in two forms, malignant and benign¹⁰ In young persons the severity seems much greater than in older persons, frequently eventuating fatally The older patient may be asymptomatic and his illness often discovered by accidental roentgenographic examination

SIGNS AND SYMPTOMS

The outstanding feature of the disease is the high incidence of fractures following trivial injury Fortunately, they usually heal without difficulty, although in some patients delayed union or nonunion occurs, and the incidence of osteomyelitis at these fracture sites is higher than normal⁸ Commonly one sees delayed dentition and dental caries which often lead to abscesses and osteomyelitis of the jaw It is believed that the bones are less resistant to infection as a result of the dense bony overgrowth which crowds out protective vascular elements¹¹ This is a serious complication and may lead to death or remain as a chronic indolent infection

Frequently one sees hepatosplenomegaly and generalized lymphadenopathy associated with severe anemia, a common observation in infants Often the patient complains of loss of sight, deafness or paralysis of muscles supplied by cranial nerves, all attributed to narrowing of the cranial foramina with resultant nerve atrophy Hydrocephalus is common in children⁸ It is believed that the small cranial foramina produce increased intracranial pressure by obstructing venous outflow Another explanation is that the vascular distention causes hemorrhage, with formation of a chronic subdural hematoma¹²

REPORT OF A CASE

L W, an unmarried white woman, aged 37, was first seen at the surgical outpatient clinic in November 1946, complaining of headache, lightheadedness and multiple contusions following a fall five days previously

8 Pehu, M, Guichard, A, and Jeune, M La maladie des os de marbre et les syndromes marmoreens, *J de med de Lyon* **27**:173-200, 1946

9 Jenkinson, E L, Pfisterer, W H, Latteier, K K, and Martin, M E A Prenatal Diagnosis of Osteopetrosis, *Am J Roentgenol* **49**:455-462, 1943

10 McPeak, C N Osteopetrosis Report of Eight Cases Occurring in Three Generations of One Family, *Am J Roentgenol* **36** 816-829, 1936

11 Winter, G R Osteosclerosis Fragilis (Albers-Schonberg's Disease) Two Cases, *Am J Orthodontics* **31** 637-649, 1945

12 McCune, D J, and Bradley, C Osteopetrosis (Marble Bones) in an Infant Review of the Literature and Report of a Case, *Am J Dis Child* **48**: 949-1000 (Nov) 1934

Questioning revealed that she had a chronically draining right ear, the discharge from which had become bloody since the fall, but this did not seem unusual to her since, as she stated, this always happened when she had a "cold," as was the case at the time of examination

The personal history revealed nothing of significance except for a mastoid infection on the right side eighteen years prior to examination This had been

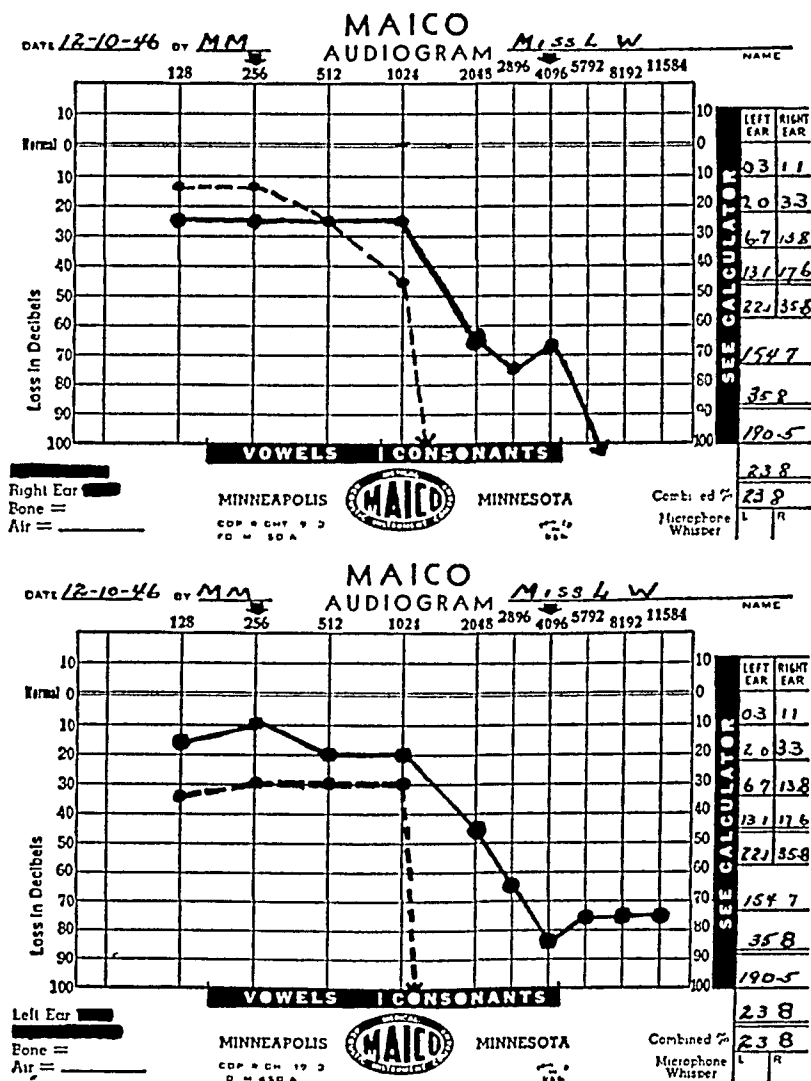


Fig 1—Audiograms of both ears, showing decided loss of both bone and air conduction above 1,024 double vibrations, indicative of inner ear deafness. The upper audiogram is of the right ear, and the lower audiogram is of the left ear

accompanied with mild progressive deafness during the past ten years. There was no recollection of any fracture.

The family history likewise revealed nothing of importance. She was an only child. There was no knowledge of parental consanguinity, of maternal abortions or of any bone disease in any relatives.

Physical examination showed a dull lethargic well developed white woman, who appeared to be her stated age. The pulse rate and respirations were normal, the temperature was 96 F and the blood pressure 115 systolic and 60 diastolic.

The eyes were normal as to pupillary size and reaction, fundi and visual fields. The right ear drum showed multiple scarring and a perforation in the posterior inferior quadrant. The Weber test elicited lateralization to the right. Audiograms (fig 1) confirmed that deafness was present, with a total loss of hearing of 23.8 per cent—35.8 per cent in the right ear and 22.1 per cent in the left.

The type of curve was characteristic of an inner ear deafness, with loss in the higher frequencies. The remainder of the physical examination was noncontributory.

Psychologic examination revealed the patient to be lacking in initiative and rather self conscious. She had prepared herself to become a teacher, but had never become active in this work. Her service in the government for the past three years had been acceptable. Socially she was a quiet retiring person who had few friends and spent most of her time reading. At times she felt "despondent and blue." The fact that her mother had been confined to a mental institution for the past thirty years was a source of concern to her, with respect to her own future.

In talking with her it was evident, even allowing for her deafness, that she was dull, bewildered and slow in responses. She seemed to have difficulty comprehending directions and took a passive attitude, with little show of emotional responsiveness. At times she appeared mildly depressed, but for the most part her emotional reactions were shallow and apathetic. Psychologic testing showed her to have average intelligence, with some limitation in comprehension and concentration. Personality tests indicated limitation of emotional drive and responsiveness.

It was felt that there were definite disturbances in this woman's emotional reactions and personality makeup. It was difficult to tell whether these were of recent origin or had existed for many years. It was indicated that she was limited in her effective adjustment to life, that she lacked initiative in her work and that she had limited social participation. The personality picture suggested schizoid characteristics.

Laboratory Studies—The urine was normal except for the observation of *Trichomonas vaginalis*. Examination of the blood revealed 4,300,000 red blood cells, 8,050 white blood cells and hemoglobin 12.5 Gm, or 86 per cent (Sahli). The cell volume was 44 per cent, or 104 per cent of normal. The color index was 1.0, the volume index 1.2 and the saturation index 0.81. The mean cell volume was 102 cubic microns, the mean cell hemoglobin 29 micromicrograms and the mean cell hemoglobin concentration 28 per cent. The differential count revealed 30 per cent lymphocytes, 4 per cent monocytes, 63 per cent neutrophils, 3 per cent eosinophils and 239,000 and 250,000 platelets. Kahn and Mazzini reactions were negative. The sedimentation rate was 11 mm (Cutler) per hundred cubic centimeters. In the fragility test, the patient's beginning hemolysis was 0.44 per cent sodium chloride and complete hemolysis 0.34 per cent sodium chloride, with the control showing beginning hemolysis 0.44 per cent sodium chloride and complete hemolysis 0.34 per cent sodium chloride. The prothrombin time of the patient was 12 seconds, or 80 per cent, and the control 15 seconds. Nonprotein nitrogen was 34.0 mg per hundred cubic centimeters. The cholesterol was 148 mg and the calcium 11.8 mg per hundred cubic centimeters. Inorganic phosphorus was 2.8 and alkaline phosphatase 2.8 Bodansky units. The basal metabolism rate was —12 per cent.

Roentgenologic Studies—In the skull (fig 2) there was a decided increase in density of the base and decided thickening of the bones of the cranial vault, with

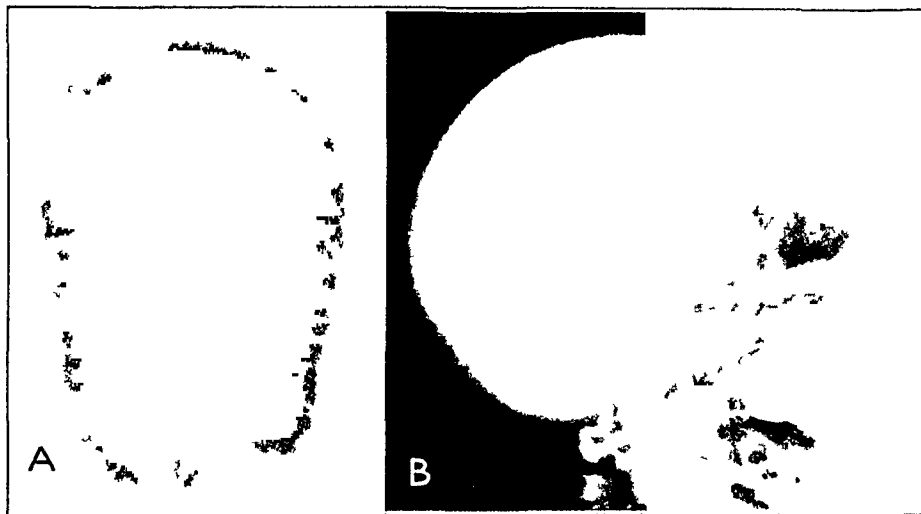


Fig 2—*A*, thickening of the cranial vault, indicating that intramembranous ossification was also affected. *B*, extraordinary denseness of the base of the skull and associated posterior clinoid "clubbing."



Fig 3—Roentgenogram of the thoracic aspect of the spine, showing the extreme calcification of the vertebrae

no differentiation between the outer and inner tables and total effacement of the diploic portion. The petrous portions of the temporal bones were decidedly dense,

and no mastoid air cells could be differentiated. The sella turcica was well formed, but the posterior clinoids were thickened, with bulbous clublike extremities. Both sides of the mandible manifested hypermineralization but there was still some semblance of trabeculation discernible.



Fig 4—Roentgenogram of the pelvis, showing the decided density of all bones except the iliac crests where there was a tendency to osteoporosis.



Fig 5—Roentgenograms of the humerus (A) and the femurs (B), showing the tendency toward thickening of the upper third of the humerus and the lower part of the femurs.

The ribs, the dorsal and lumbar portions of the spine (fig 3) and the upper halves of both humeri showed involvement similar to the changes in the mandible.

There was also the same type of hypermineralization, but with defacement of normal architecture, in the bones of the pelvis (fig 4) and in both femurs (fig 5). The upper halves of the tibiae and fibulae were similarly involved, and these bones showed some lack of normal modeling or tubulation.

CAUSATION OF OSTEOPETROSIS

In osteopetrosis so many factors have been considered as causal agents and with such frequency that none can be omitted. The most prominent factor is heredity. The high incidence of the disease in parents and grandparents of patients suffering from the disease and the

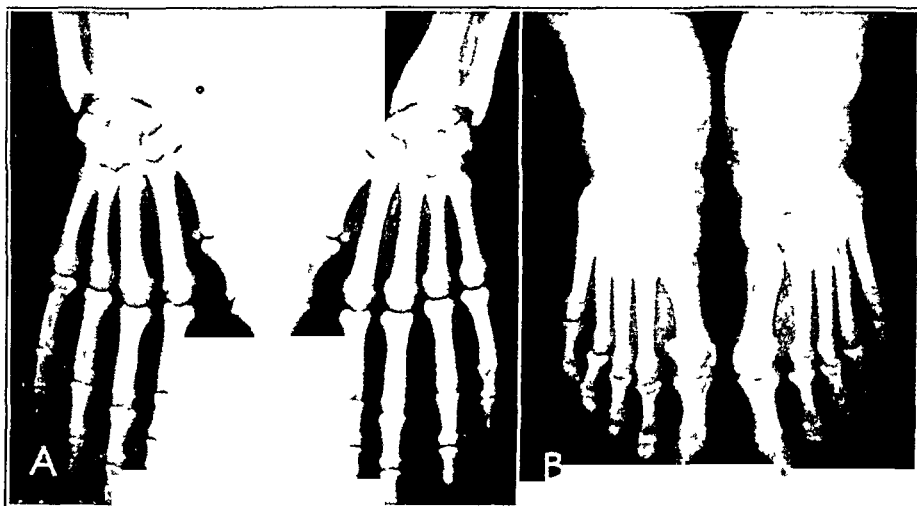


Fig 6—Roentgenograms of the hands (A) and the feet (B), revealing the generalized hypermineralized condition of bone.

presence of the condition in infants and young children cannot be overlooked. McPeak¹⁰ reported the occurrence of the disease in 8 members in three generations of one family. Pirie,³ Higinbotham and Alexander¹³ and, most recently, Kelley and Lawlah¹⁴ have reported occurrence in 1 or more members of a family. That some hereditary factor, regarded by most authors as a mendelian recessive trait, is at play seems probable.

Inasmuch as the osseous and the hemopoietic systems have a common origin, an undifferentiated mesenchyme, it would seem probable that the pendulum could swing either way in favoring growth of these two systems. Thus, when the primitive marrow cavity is formed and blood vessels, carrying with them undifferentiated tissue, grow in from

13 Higinbotham, N. L., and Alexander, S. F. Osteopetrosis. Four Cases in One Family, *Am J Surg* 53:444-454, 1941.

14 Kelley, C. H., and Lawlah, J. W. Albers-Schonberg Disease. A Family Survey, *Radiology* 47:507-513, 1946.

the periosteum, there is the inherent power present for this tissue to develop into osseous or hematogenic elements. In this case osteogenesis is favored at the expense of the hemopoietic system. On the opposite balance of the scale is offered osteogenesis imperfecta as an example of decreased bone production. In this condition, the bones are narrow and rarefied and the individual trabeculae are thin. This disease is believed to be hereditary in nature and, like osteopetrosis, has been diagnosed in utero. Another interesting analogy between these two diseases is that both present an early fulminating type, the so-called malignant type, that develops early in life with such devastating effects and a latent much less severe type, the so-called benign form, that appears to start, or at least is discovered, in adults.

In 1936 Spéder,¹⁵ having discovered osteopetrosis in a Moroccan native, was impressed with its similarity in regard to bony changes to a disease in animals known as "darmous," which occurs in areas where the drinking water contains small quantities of fluorides and phosphorus. It is known that osteomyelitis of the mandible and late, as well as faulty dentition associated with dental caries are common symptoms of both osteopetrosis and chronic fluorosis. Therefore, Spéder made roentgenologic studies of the skeletons of 6 such natives presenting severe dental disturbances and observed in all bony changes similar to osteopetrosis.

Bishop¹⁶ in the same year made a complete roentgenologic study of the bony changes in a human being suffering from chronic fluorine poisoning and thirteen and a half months later was fortunate enough to secure a postmortem study of this person. The essential roentgenographic changes he reported were an increase in bone density, with no alleviation in bone structure, lack of normal sharpness of bone outline and extension of calcification into ligamentous attachments. On subsequent microscopic study the haversian canals were observed to be plugged with calcium fluoride crystals. The chemical analysis of segments of the various bones and neighboring deposits showed a fluorine content that varied from 0.29 to 0.68 per cent (method of Willard and Winter). The bones showing the highest fluorine content were the densest roentgenographically. Normal fluorine content of bone is 0.03 to 0.07 per cent of fluorine.

15 Spéder, E. L'osteopetrose generalisee ou "marmoskelett" n'est pas une maladie rare. Sa frequence dans l'intoxication flourée, J de radiol, et d'electrol **20**:1-11, 1936, abstracted, Am J Roentgenol **38** 506, 1937.

16 Bishop, P. A. Bone Changes in Chronic Fluorine Intoxication, Am J Roentgenol **35** 577-585, 1936.

The studies by Kramer and his co-workers¹⁷ and Clifton and his co-workers¹⁸ show that the bones in patients with osteopetrosis contain only normal chemical constituents, with merely a higher carbonate content associated with hypermineralization. Furthermore, there is individual trabecular thickening and numerical increase, with loss of normal architecture not seen in chronic fluorosis. Also, the extension of calcification to soft tissue, ligaments and cartilage, seen only in the latter, is a further differential feature.

Though all glands of internal secretion have been incriminated at one time or another, perhaps the only one which might bear some relationship to osteopetrosis is the parathyroid. A great deal of interest was aroused over this possibility when Péhu and his co-workers¹⁹ observed a parathyroid adenoma in their patient with osteopetrosis.

In 1932 Selye,²⁰ who administered parathyroid hormone experimentally to rats over a prolonged period of time, made some interesting observations. At first he noted the typical signs of osteitis fibrosa cystica, with the usual outpouring of osteoclasts, bony decalcification and resorption, marrow fibrosis and associated mobilization of calcium. This was followed, however, by a secondary stage of osteoblastic proliferation, beginning at the metaphysis and resulting in a dense bony overgrowth which was strikingly similar to that seen in osteopetrosis.

Furthermore, he observed that this primary phase of osteoclasts and calcium mobilization could be omitted if he gave small doses of parathyroid hormone, the rats showing signs of osteoblastic activity only.

Along similar lines, Pugsley and Selye²¹ studied the effects of 20 units of parathyroid hormone, administered daily, on the calcium levels in the blood and urine, as well as associated osteoclastic and osteoblastic activity. They observed that when the maximum number of osteoclasts was present, the levels of calcium in the blood and the urine reached their peak and that as the osteoclasts disappeared these levels correspondingly fell, until on the twelfth day, when osteoclasts were practically absent, they returned to normal. Osteoblastic activity began

17 Kramer, B., Yuska, H., and Steiner, M. W. Marble Bones. Chemical Analysis of Bone, *Am J Dis Child* **57** 1044-1057 (May) 1939.

18 Clifton, W. M., Frank, A. A., and Freeman, S. Osteopetrosis (Marble Bones), *Am J Dis Child* **56** 1020-1036 (Nov) 1938.

19 Péhu, M., Policard, A., and Dufourt, A. L'osteopetrose ou maladie des os marmoreens, *Presse med* **39** 999-1003, 1931.

20 Selye, H. On the Stimulation of New Bone Formation with Parathyroid Extract and Irradiated Ergosterol, *Endocrinology* **16** 547-557, 1932.

21 Pugsley, L. I., and Selye, H. The Histological Changes in the Bone Responsible for the Action of Parathyroid Hormone on the Calcium Metabolism of the Rat, *J Physiol* **79** 113-117, 1933.

on the fourth day, in appreciable amount, and was constantly augmented thereafter. From this it would seem that as a result of parathyroid stimulation large numbers of osteoclasts are formed which phagocytose bone, thus shifting the calcium into the blood and the urine.

As to the actual role of the osteoclasts, much confusion exists,²² for one school claims that the parathyroid hormone acts directly on the bones stimulating osteoclasts and the other claims that the presence of a large number of osteoclasts is not a specific hormonal reaction because it can be produced by procedures other than parathyroid stimulation. Thus, the latter group holds that the osteoclast phagocytoses the bony matrix only after decalcification has occurred. To us the former theory seems to be the likeliest, considering the evidence offered in osteopetrosis with administration of parathyroid injection producing little or no response, there is no hypercalcemia, nor is there any increased urinary excretion of calcium. None have attempted to explain this unusual phenomenon, however, when one considers the histologic picture, in which there is a definite paucity of osteoclasts²³ and, no doubt, an inability to form osteoclasts²⁴ in large quantity, it seems logical that parathyroid stimulation will not effect any mobilization of calcium.

In human beings suffering from osteopetrosis many estimations of blood elements have been made, few observers, however, have performed calcium and phosphorus metabolic studies. As a whole, calcium and phosphorus blood levels have been within normal limits except when associated with some other disease such as rickets. Flood²⁵ reported a serum calcium determination of 16.2 mg per hundred cubic centimeters, which was the only elevated value observed. Several low levels of phosphorus in the serum have been seen in infants. However, in all, active or healing rickets was present, making difficult a decision as to the cause of such observations. It might also be emphasized at this time that it does not seem logical to compare the disease in adults, which presumably may be in the resting stage, with the disease in infants, in whom the disease process is active.

22 Cantarow, A., and Trumper, M. *Clinical Biochemistry*, ed 3, Philadelphia, W. B. Saunders Company, 1945, p. 173.

23 (a) Pirie³ (b) Jenkinson Pfisterer, Latteier and Martin⁹ (c) Clifton, Frank and Freeman¹⁸ (d) Selye²⁰ (e) Zwerg, H. G., and Laubmann, W. *Die Albers-Schonbergsche Marmorkrankheit*, *Ergebn d med Strahlenforsch* 7: 95-136, 1936.

24 Krompecher, S. *Die Chondroklasie, normal und pathologisch, namentlich bei Marmorknochenkrankheit. Die Bedeutung und Funktion der Osteoklastenriesenzellen*, *Beitr z path Anat u z allg Path* 104: 164-185, 1940.

25 Flood, R. G. *Calcium Metabolism in Marble Bone (Albers-Schonberg Disease)*, *California & West Med* 31: 203-204, 1929.

Concerning studies of calcium-phosphorus balance, it has been observed that the percentage of retention of these minerals is extremely high, as would be expected

A summary of these studies appears in the table

Summary of Reports of Calcium-Phosphorus Balance in the Literature

Author	Calcium Retention (Percentage)	Phosphorus Retention (Percentage)
Flood ²⁷	33	
McCune and Bradley ¹²	65-83 (healing rickets)	37-47
Pincus, Gittleman and Kramer ²⁶	60 (healing rickets)	47
	59 (active rickets)	37
Clifton ¹⁸ .. ---- ..	50	

Attempts to effect a negative calcium balance have been unsuccessful except those of Flood,²⁵ and he was on one occasion able to cause a loss of only 0.1098 Gm of calcium by administering 25 units of parathyroid extract every thirty-six hours

As a whole, excretion of calcium was almost entirely via the stool. In the cases of Pincus and his co-workers²⁶ and Flood,²⁵ 99 per cent of the calcium elimination was seen in the stool. This is extremely high, especially in view of the fact that there was no apparent reason. Pincus and his co-workers specifically denied the presence of any intestinal disorders. Flood observed no evidence of rickets. Of the patients of Pincus, 1 was suffering from active rickets, which would explain such a value (it is believed that in rickets and osteomalacia, although defective absorption plays an important role, the seat of trouble is defective intermediate calcium and phosphorus metabolism, so that normal ossification cannot take place, and as a result an increased amount of calcium is eliminated into the lower bowel), however, the disease in the other infant was definitely in the healing zone where one would expect a diminution in the amount of calcium in the stool, more being excreted in the urine.

Studies of phosphorus excretion were carried out by Pincus and his co-workers²⁶ and McCune and Bradley.¹² Their results coincide rather closely, in that in all 3 children studied about 80 per cent of the phosphorus excreted was seen in the urine. This is a characteristic of the healing stage in rickets, for which 2 of the infants were undergoing treatment. However, in a case such as that of Pincus and his co-workers, in which florid rickets existed, such an observation is unheard of. This led Pincus and his associates to postulate some increased parathyroid activity (a rise in urinary phosphorus being a cardinal laboratory characteristic of this disease).

²⁶ Pincus, J. B., Gittleman, I. F., and Kramer, B. Juvenile Osteopetrosis: Metabolic Studies in Two Cases and Further Observations on the Composition of the Bones in This Disease, *Am J Dis Child* 73: 458-472 (April) 1947.

That osteopetrosis is caused by increased parathyroid activity, no matter how small, seems rather doubtful, that there is some secondary stimulation of the parathyroid glands, however, seems probable

When one considers the hereditary character of the disease, the generalized involvement with the attack on the hemopoietic system, the enlargement and fibrosis of the lymph nodes, the hepatosplenomegaly, the normal appearance of the parathyroid glands and the lack of laboratory evidence, such as hypercalcemia, elevated level of alkaline phosphatase in the serum and decided hypercalcuria, one can exonerate the parathyroid glands as the primary cause of the disease. However, such generalized bony changes and the observation of an elevated level of phosphorus excretion in the urine certainly point to some secondary parathyroid involvement

Jongherr and Landauer²⁷ in 1938 reported an endemic outbreak of hypertrophic osteopathy in chickens. This spontaneous disease affected birds of both sexes and various breeds, usually between the ages of 4 and 6 weeks, causing thickening of the diaphysial sections of the leg and wing bones with the exception of the phalanges. These changes were usually associated with lesions of leukemic lymphomatosis. Histologic sections of the bones revealed a striking similarity to that seen in the human entity, being characterized by diffuse thickening of the substantia spongiosa and substantia corticalis accompanied with hypercalcification and narrowing of the medullary cavity. Microscopically there was noted lack of endochondral ossification, hypercalcification of nonlamellated interstitial connective tissue bone and marrow fibrosis. The trabeculae were hypertrophied and presented a mosaic structure with loss of normal architecture. Osteopetrosis gallinarum was suggested as a name for this condition, because of its resemblance to the condition in human beings. They divided the condition into three stages: initial, florid and resting. On further experimentation they observed that the disease could be reproduced by inoculating baby chicks with tissue from subjects with the disease in the florid stage only. This transmissible agent appeared to be present in blood, bone marrow and lymphomas. Sixty-one chicks were inoculated with the production of 6 subjects with gross lesions.

In similar work on chicks Burmester, Prickett and Belding,²⁸ using the RPL¹-12 lymphoid tumor strain, obtained results closely paralleling those previously mentioned.

27 Jongherr, E, and Landauer, W. A Condition Resembling Osteopetrosis (Marble Bones) in the Common Fowl, Bulletin 222, Storrs Agricultural Experiment Station, 1938

28 Burmester, B. R., Prickett, C. O., and Belding, T. C. A Filterable Virus Producing Lymphoid Tumors and Osteopetrosis in Chickens, Cancer Research 6: 189-196, 1946

They set up tests employing cell-free centrifuged suspensions of ground up lymphomas, the cell-rich sediment from them, as well as the blood cells and the plasma, which were filtered through a Sietz sterilizing filter pad. Inoculations of the 2 and the 3 day old chicks with these substances brought about the following results. The birds inoculated with viable cells died within a short time (two to ten days) of local and visceral tumor metastases. However, the chicks inoculated with the cell-free preparations, whether filtered or centrifuged, showed no pathologic condition until at least 10 weeks of age, at which time they began to exhibit signs of osteopetrosis, and by 6 months 41 per cent were affected with the malady. Fifty-six per cent of the birds presented microscopic visceral tumefactions, the liver was especially involved in these cases. A total of 80 birds were inoculated with cell-free preparations, and in 84 per cent there developed visceral, neural or bone involvement which was evident on gross examination. Of the 65 birds showing pathologic changes, 20 had osteopetrosis without gross evidence of other pathologic lesions. Twenty-nine had visceral tumors without osteopetrosis, and 16 had both. The average life span was 144 days.

Autopsy and histologic section revealed changes as described previously by Jongherr and Landauer²⁷

These observations are suggestive of a filterable substance, whether it be a virus in the true sense of the word or some other entity which may be the *modus operandi* in the disease in human beings. Further study and application to human beings must be made before any such tenet can be held with certainty.

Whatever is the cause of this disease—hereditary, viral or viroid, calcium-phosphorus imbalance or hormonal—the studies are intriguing and pregnant with potentialities. To our way of thinking the filterable substances offer the likeliest explanation.

DIFFERENTIAL DIAGNOSIS

With the fully developed syndrome of hepatosplenomegaly, anemia, multiple fractures, cranial nerve involvement, a carefully made and complete history, as well as a composite roentgenographic study of the skeleton, the diagnosis of osteopetrosis is not difficult.

Some of the uncommon conditions, as condensing osteitis of Sicard, eburnizing osteitis of Putti, ivory vertebra and meloreostosis, may present a problem, but, since these conditions are not generalized, a complete study of the skeletal system disposes of them. This will also exclude and differentiate osteopetrosis from leontiasis ossea, Paget's disease and osteitis fibrosa cystica.

Physiologic osteosclerosis of newborn infants and congenital syphilis have to be considered. The former is believed to represent a

physiologic storage of calcium and, like osteopetrosis, includes the entire osseous network. The increased density of the bones disappears in the course of the first few weeks of life, so that repeated roentgenologic studies will show decreased density. Congenital syphilis also shows osteosclerosis, but gives definite evidence of decided thickening of the periosteum, areas of destruction in the region of metaphysis and most characteristically does not attack the bones of the base of the skull. Serologic studies aid in establishing this diagnosis.

Interestingly enough, offspring of persons in any way associated with fluorine poisoning may show changes of the sclerotic type. But here, as in chronic fluorine poisoning, the architecture of bones remains unchanged and the adjacent soft tissues show osteophyte formation with calcification of intervertebral ligaments and periosteal deposits.

In the early stages of osteopetrosis it may be difficult to differentiate from lead poisoning, but if roentgenograms are taken of the feet and the skull, the differential diagnosis can probably be made, as the astragalus and sphenoid reveal evidence of marble bones early in the disease, whereas in lead poisoning there will be no evidence of changes in these bones. Chronic poisoning with lead and phosphorus show definite dense bands across the metaphysis in roentgenograms. Administration of vitamin D has also been reported to result in this phenomenon. In this metallic group of diseases, history, chemical analysis and microscopic examination of the blood establish a diagnosis.

The myelophthisic anemia in osteopetrosis does not differ notably from that in leukemia, but in this hematologic disease the bone changes are predominantly infiltrative and destructive. If there is involvement of the periosteum, the density is not so great and the extent of involvement is never so universal. The large number of nucleated red cells suggests familial erythroblastic anemia or a crisis in the course of familial hemolytic icterus. The roentgenogram of patients with familial erythroblastic anemia (Cooley's anemia) is characteristic, and there never have been reports of altered fragility in osteopetrosis, nor is its blood picture characterized by the presence of an abnormal number of microcytes.

Patients with cancerous metastasis or primary malignant conditions exhibit roentgenographically increased density, but only in isolated areas of the osseous system.

The most prominent symptom, namely, multiple fractures, may present some confusion with osteogenesis imperfecta, but roentgenograms in this disease show a lessened rather than increased density, although it also is generalized.

ROENTGENOLOGIC ASPECTS

Roentgenologically considered, osteopetrosis is a skeletal dystrophy in which increase in the density of the roentgenographic shadow cast by bone is the most characteristic feature. This increase is generalized and in typical cases is rather startling. The usual architectural features of normal bone, such as fine trabeculations of the substantia spongiosa, well proportioned cortices and marrow cavities, careful modeling or tubulation and sharply contrasting densities, are missing. The building of osteopetrotic bone appears to have been sublet to an amateurish contractor, who had an abundance of mineral salts available and used them with a lavish, if untrained, hand.

While the long bones, ribs and pelvis are the structures most commonly involved, the head, the spine and the bones of the hands and feet are frequently seen to manifest the changes of this disease.

The density of the shadows cast by these bones, as has been pointed out in the work of Kramer and his co-workers¹⁷ and Clifton and his co-workers,¹⁸ is due to the hypermineralization with normal chemical constituents. The lack of resorption of calcified cartilage, as is readily demonstrated histologically, further explains this increase in density in those bones preconceived in cartilage. Osteopetrotic changes, however, also occur in membranous bones, e.g., the bones of the calvarium, the ribs and the clavicles.

The roentgenographic picture varies with the severity of the disease. In the milder type of disease, first discovered when the patient has attained adult age, there may be little more than uniform increases in the density of the bones of the base of the skull, the spine and the pelvis. In the florid disease of early childhood, the entire skeleton may be involved and grossly disfigured.

While decidedly dense, osteopetrotic bone is not always uniformly so. Striking variations often occur in the shafts of the long bones, the carpal and tarsal bones and in the flaring portions of the iliac bones. At times translucent bands of decreased density of varying width are seen near the epiphyseal plate and often extending well up the diaphysis. These are transverse strata of defective loose substantia spongiosa. They represent a period of growth in which excessive destruction of cartilaginous lattice has occurred and are somewhat of a paradox in osteopetrosis. Certainly some interruption or temporary cessation of the usual course of events in the laying down of osteopetrotic bone has occurred.

In other cases, there are longitudinal streakings and transverse striations of heavy density. These are probably only expressions of

arrested growth and, as has been demonstrated by the work of Harris,²⁹ may be met with in almost any systemic disease in which there is nutritional impairment for any length of time

The faulty tubulation or modeling of the long bones, manifested most characteristically by heavy clublike expansion of the lower half of the shaft of the femur or upper half of the shaft of the humerus, is another interesting observation in osteopetrosis. That this type of deformity should occur is feasible, since it is well recognized from histologic studies that there is a paucity of osteoclasts in osteopetrotic bone. It is the activity of these cells, with the aid of the restraining influence of an intact periosteum, that effects the nicely turned symmetric normal long bones.

The frequency of rickets seen in association with osteopetrosis is noteworthy. Several of the observations which we have just discussed, such as translucent bands, arrested growth lines and faulty tubulations, are just as common to rickets as they are to osteopetrosis.

The frequent association of osteopetrosis with osteomyelitis and delayed dentition are probably attributable to an impaired vascular supply, and consequently the nutritive requirements for normal development and maintenance of a healthy state are inadequate.

Fractures, likewise, are a common observation in the patient with osteopetrosis. These usually heal with the production of adequate, and at times, abundant, callus. However, delayed union is not unusual. Evidence of healed or healing fractures has been discovered with the patient having been unaware of their occurrence.

There are numerous references in the literature to the clublike thickening of the posterior clinoid process and narrowing of the sella turcica. It is claimed by some that these¹² are invariable observations and that one should hesitate to confirm a diagnosis of osteopetrosis in their absence. This, we believe, is a broad statement in light of the numerous types of sellae that we routinely see in the course of our daily work.

Ordinarily, the base of the skull is first and most decidedly affected by this disease. The bones of the calvarium, however, may also be involved and become so uniformly dense that no distinction can be made in the tables and the diploic portion. Obliteration and effacement of the mastoid cells and air spaces of the paranasal sinuses are fairly common. Narrowing of the various foramina of the skull, with compression of the corresponding emerging nerves, is not rare.

29 Harris, H. A. *Bone Growth in Health and Disease. The Biological Principles Underlying the Clinical, Radiological and Histological Diagnosis of Perversions of Growth and Disease in the Skeleton*, London, Oxford University Press, 1933.

PATHOLOGIC ASPECTS

The pathologic condition is limited to the hemopoietic system, the bones and the structures supplied by cranial nerves, as well as the cerebrum and the meninges

The optic is the only cranial nerve that is affected with any frequency. However, deafness is common.

Hydrocephalus, thickening of the meninges and chronic subdural hematomas are frequently seen in children. Their production is explained on the theory that the narrowed cranial foramina increase the intracranial venous pressure, which may lead to bleeding with formation of chronic subdural hematoma or which will elevate the cerebrospinal fluid pressure, either of these eventuating in the formation of hydrocephalus.¹²

The liver, spleen and lymph nodes frequently show hypertrophy, in spite of which hematopoiesis is depressed, the enlargement being due in greater part to excessive fibrosis. Furthermore, the degree of anemia seems to parallel the size of these organs. There is no correlation between the roentgenographic appearance of bone and the anemia, for there are cases on record with complete obliteration of the marrow cavity, seen roentgenographically, with an essentially normal blood picture.

The peripheral blood has no characteristic features. The erythrocyte usually shows no changes except in size and volume, and these are not constant. Terminally, there may be hypoplastic anemia. Occasionally immature red cells may be seen, mostly normocytes. Platelets as a rule are not diminished. The leukocyte count may be normal or reduced. Infants, being more prone to leukocytosis than adults, may show young cells, mostly of the myeloid type.¹²

The bones offer the most interesting pathologic changes. Grossly, they appear white and brittle. Pirie,³ in studying the resistance offered to a surgical drill by marble bone and a piece of chalk, expressed the belief that the latter cut with much more difficulty. Many surgeons, however, in working with these bones, insist that they are harder than normal. It is debatable, therefore, whether the frequency of fracture is due to the softness or to the loss of internal architectural elasticity.

Characteristically, the bones are thickened and encroach on the marrow cavity to the extent that it may be but a pinpoint. Also, the total circumference of the bones may be enlarged. This is especially seen in the clublike thickening of the upper third of the humerus and the lower end of the femur. On cross section, the bone may have a homogeneous dense appearance, with loss of differentiation between the *substantia compacta* and the *substantia spongiosa*. This is especially seen at the metaphysis. The marrow cavity and marrow spaces are naturally diminished, and what remain show extreme fibrosis, with loss of hemopoietic tissue similar to that of the other blood-forming organs previously mentioned.

HISTOLOGIC ASPECTS

Instead of the widely fenestrated delicate cartilaginous and later bony trabeculation, forming the primary spongy type of bone, one sees a predominantly solid calcified cartilaginous matrix in which numerous small irregular open spaces exist. Pirie³ stated that these spaces comprise less than 25 per cent of the total structure. They are filled entirely or in part by amorphous primitive bony plaques.

The cause for this is revealed, in the work of Krompecher,²⁴ who stated that the cartilage cells, which normally swell and become rather large, remain small, thus leaving a large amount of hyaline matrix and small cellular spaces.

As is known, primitive mesenchymal and vascular connective tissue derived from the embryonic marrow cavity migrates into the provisional zone of ossification, burrowing paths through the calcified cartilaginous bars, and gains entrance to the large cavities left by the necrotic cartilage cells. One can easily see, then, that it is much more difficult for primitive marrow to gain entrance to this thick calcified hyaline structure than to the delicate honeycomb of normal cartilage, also, where penetration has occurred, the spaces are so small that, instead of the usual three or four layers of osteoblasts arranging themselves around a central large cavity, only one or two layers are possible and the central cavity is crowded, so that there is little chance for hemopoietic tissue to develop, especially the large giant cells or osteoclasts, which are uniformly reported to be conspicuously diminished in number.³⁰

It is evident, then, that true bone formation is impossible, and, as a result one sees broad areas of calcified cartilage, some of which contain within them true bone and similarly wide expanses of fibrous tissue containing centrally islands of bone, both apparently due to metaplasia.³⁰

Many authors have reported an increased amount of osteoid,³¹ the significance of this is unknown. Whether it is related to a vitamin deficiency or rickets has not been established. Clinically, rickets has been reported in combination with this disease, and the persistence of insulae of calcified hyaline cartilage in the metaphyses common to rickets has been seen.¹⁸

The marrow cavity and marrow spaces show fibrosis of varying degrees. This is one of the pathognomonic signs of the disease and is a constant observation.

30 (a) Pirie³ (b) Jenkinson, Pfisterer, Latteier and Martin⁹ (c) Krompecher²⁴ (d) Zwerg and Laubmann^{23c} (e) Kijksra, O. H. L'osteogenèse dans la maladie des os marmoreens, *Ann d'anat path* 12 131-141, 1935

31 Pirie³ Jenkinson, Pfisterer, Latteier and Martin⁹ Clifton, Frank and Freeman¹⁸ Herscher, H., and Stein, J. J. Osteopetrosis Associated with Hodgkin's Disease. Review of the Literature and Report of a Case, *Am J Roentgenol* 43 74-80, 1940

Though this theory holds for the intracartilaginous development of bone, it certainly does not explain why the flat bones, developed within a membrane, are also affected. One must postulate then that, besides the disturbance in cartilage resorption, there is also an inability of true bone to form and assume normal structure. Instead one sees the heavy overgrowth of amorphous bony tissue previously described, blotting out diploe and marrow spaces in the flat bones.

PROGNOSIS AND TREATMENT

In the infant the outlook for life is generally poor, with death resulting from extreme inanition and intercurrent infection. Those who do survive usually have the stigmas of blindness, deafness, hydrocephalus, anemia and multiple fractures. In the adult, except for anemia and multiple fractures, the prognosis is generally favorable. Osteomyelitis is a serious complication. The treatment is ineffective. Several attempts have been made to mobilize calcium, without success.

SUMMARY

A case of osteopetrosis is presented, with complete laboratory and roentgenographic examination.

The causation is reviewed, with special attention to the possibility of a viroid origin, as demonstrated in birds.

Special attention is paid to the role of the cartilaginous precursor of bone in the development of this disease.

ASSOCIATION OF HEPATIC INSUFFICIENCY WITH CHRONIC ULCERATIVE COLITIS

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THE OCCURRENCE of disease of the liver in association with chronic idiopathic ulcerative colitis has received little emphasis. Pylephlebitic abscess is occasionally listed as an uncommon, but fatal, complication of ulcerative colitis¹ but nonsuppurative parenchymal hepatic disease is rarely mentioned. However, as early as 1899 Lister² reported a case of diffuse ulcerative colitis associated with a secondary acute interstitial hepatitis characterized by a diffuse cellular infiltration in the liver and the presence of an abundance of "fat globules." It is of interest to note that even before the separation of "simple ulcerative colitis" from the dysenteries by Wilks and Moxon,³ Thomas⁴ reported a fatal case of ulceration of the colon in which the rapidly fatal termination was felt to be due to a pathologic process in the liver. The liver was described as being enlarged to twice normal size, much softened and in an advanced stage of fatty degeneration. Logan⁵ reported the autopsy findings in 13 cases of ulcerative colitis and found 1 instance of definite portal cirrhosis and 1 instance of "panhepatitis." In 9 instances the liver showed fatty changes and in 2 cases the liver was essentially normal except for the presence of cloudy swelling and edema. Cain and others⁶ pointed out several years later that in the

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1 Bargen, J. A. *The Modern Management of Colitis*, edited by M. Fishbein, New York, Doubleday, Doran & Company, Inc., 1934.

2 Lister, T. D. A Specimen of Diffuse Ulcerative Colitis with Secondary Acute Diffuse Hepatitis, *Tr. Path. Soc. London* **50** 130, 1899.

3 Wilks, S., and Moxon, W. *Lectures on Pathological Anatomy*, ed. 2, Philadelphia, Lindsay and Blakiston, 1875, p. 408.

4 Thomas, C. H. Ulceration of the Colon with a Much Enlarged Liver, *Tr. Path. Soc. Philadelphia* **4** 87, 1874.

5 Logan, A. H. Chronic Ulcerative Colitis. A Review of One Hundred and Seventeen Cases, in *Collected Papers of the Mayo Clinic*, edited by M. H. Mellish, Philadelphia, W. B. Saunders Company, 1918, vol. 10, p. 186.

slowly fatal cases of ulcerative colitis the liver is the site of a progressive fatty hepatitis. It was felt that the prognosis paralleled the state of the liver and that death occurred when the liver had undergone complete functional derangement. Other investigators⁷ recognized the occurrence of parenchymal changes in patients with ulcerative colitis coming to necropsy, and it was suggested that the severe colitis was a secondary manifestation of underlying hepatic disease. Likewise, other authors⁸ have emphasized the importance of changes in the liver in the course of chronic ulcerative colitis. Degenerative fatty changes have been particularly pointed out^{8a} but a toxic infectious hepatitis has also been described,^{8b} and since this type of change did not occur in every case of ulcerative colitis, a special clinical form of "rectocolitis with hepatic insufficiency" was postulated.⁸

In this country only two recent reports⁹ have mentioned the importance of liver disease in ulcerative colitis. Comfort and associates^{9a} described 4 cases with evidence of hepatic insufficiency. In 3 cases the colitis preceded the development of the hepatic insufficiency, but in the fourth case the hepatic insufficiency apparently occurred first. More recently Tumen and others^{9b} reported 5 cases of hepatic cirrhosis occurring as a complication of ulcerative colitis. These 5 instances of cirrhosis occurred among a total of 151 cases of ulcerative colitis. In 4 cases the diagnosis of cirrhosis was established by peritoneoscopy. It was pointed out that there was clinical evidence of cirrhosis in 4 cases, but that in the fifth case there were no clinical signs to suggest such a diagnosis. For this reason it was suggested that the routine use of liver function tests in all cases of chronic ulcerative colitis would possibly uncover a much greater incidence of hepatic injury in this disease.

6 (a) Cain, A., and Oury, P. Les colites et les recto-colites ulcereuses, *Rev crit de path et de therap* **2** 707 and 813, 1931. (b) Bensaude, R., Cain, A., and Massot, H. Les lesions de la recto-colite ulcereuse aigue, *Arch d mal de l'app digestif* **22** 127, 1932.

7 Popovici, J. D. L'Insuffisance hepatique et la colite ulcereuse grave, *Gaz med de France (supp gastro-enterol)*, 1933, p 6. Saccone, R., and Repetto, H. D. La fonction hepatica en las colitis ulcerosas, *Actas Cong nac med Rosario* **5** (pt 4) 39, 1934, *Arch argent de enferm d ap digest y de la nutricion* **10** 179, 1934-1935.

8 (a) Cain, A., and Cattani, R. Le role de l'hepatite degenerative graisseuse dans l'evolution et le pronostic des recto-colites suppurees, *Bull et mem Soc med d h6p de Paris* **53** 673, 1937. (b) Caroli, J., Busson, A., and Girard, P. Contribution anatomoclinique a l'etude de l'atteinte hepatique au cours des colites ulcereuses graves, *Arch d mal de l'app digestif* **27** 762, 1937.

9 (a) Comfort, M. W., Barger, J. A., and Morlock, C. G. The Association of Chronic Ulcerative Colitis (Colitis Gravis) with Hepatic Insufficiency, *M Clin North America* **22** 1089, 1938. (b) Tumen, H. J., Monaghan, J. F., and Jobb, E. Hepatic Cirrhosis as a Complication of Chronic Ulcerative Colitis, *Ann Int Med* **26** 542, 1946.

In view of the lack of statistical data both on the incidence and the importance of nonsuppurative hepatic insufficiency in chronic ulcerative colitis, a study was undertaken to elucidate these points. The data dealt with included 70 cases of nonfatal and 17 cases of fatal ulcerative colitis in which necropsy was performed. All patients had been admitted to the University Hospital during the last five years, and the basis for the selection of nonfatal cases for inclusion in this study was that one or more tests of liver function had been carried out. The necropsied cases were studied whether such tests had been carried out or not. In this study of a total of 87 cases a total of one hundred and twenty-nine separate tests of liver function had been made as follows: sixty-three of serum protein, twenty-seven of prothrombin time, twenty-seven brom-

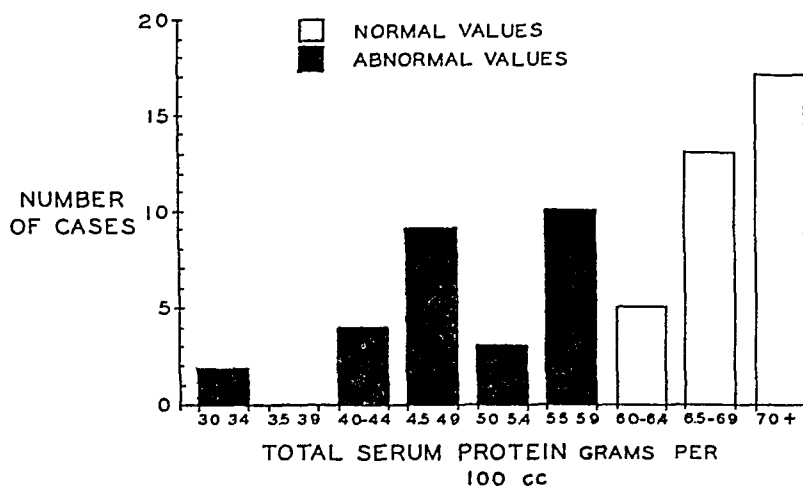


Fig 1—Total serum protein in cases of chronic idiopathic ulcerative colitis

sulfalein tests and twelve cephalin cholesterol flocculation tests. In 21 cases two or more different tests of liver function had been carried out. In the 17 fatal cases the complete autopsy findings were studied. In 4 cases a diagnosis of cirrhosis was possible, two by autopsy and two by clinical data.

STUDIES OF THE FUNCTION OF THE LIVER

Serum Proteins—Serum proteins were determined in 63 cases. The distribution of the results for total serum proteins is shown in figure 1. Values of 6 Gm per hundred cubic centimeters or higher were considered within the normal range. It will be noted that of 63 cases, 28 demonstrated abnormally low total serum proteins. Although it is generally accepted that the level of the total serum proteins may reflect the functional state of the liver, one must be cautious in applying this interpretation in all instances, particularly in chronic ulcerative colitis.

in which other factors may be operative in causing a reduction in this level. The most obvious other factor to be considered in ulcerative colitis is the nutritional status of the patient. For that reason an attempt was made to correlate the level of total serum protein with the nutritional state. This is indicated in table I in which loss of weight (employed as

TABLE 1—*Relationship Between Loss of Weight and Total Serum Proteins in 63 Cases of Chronic Ulcerative Colitis*

Number of Patients	Loss of Weight (Pounds)	Average Total Serum Proteins (Gm per 100 Cc)
1	0 - 5	6.7
3	6 - 10	6.2
4	11 - 15	6.4
9	16 - 20	6.4
18	21 - 30	5.7
17	31 - 40	6.7
11	41 plus	5.7

a general index of nutritional status) was compared to serum protein level. It will be noted that there is no such correlation. For example, in those 17 instances in which the loss of weight was between 31 and 40 pounds (14 and 18 Kg.) the average total serum level was well within normal limits. The data at least suggest that the 28 instances of abnor-

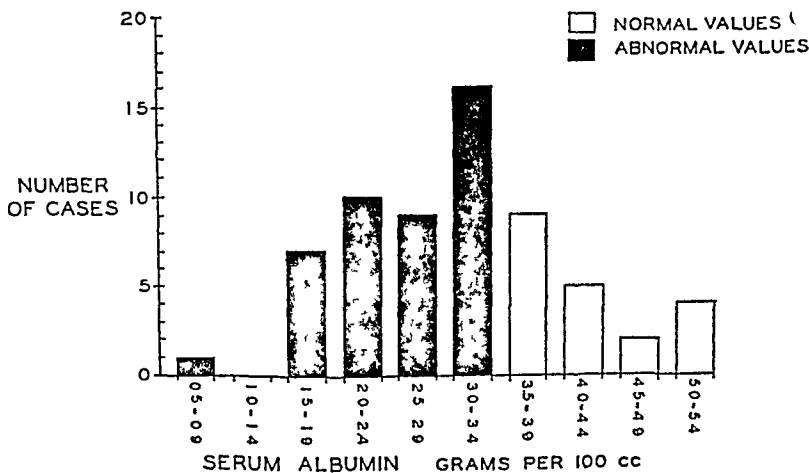


Fig. 2—Serum albumin in cases of chronic idiopathic ulcerative colitis

mally low total serum proteins are probably a reflection of hepatic insufficiency rather than nutritional deficiency.

In this connection it is well to point out that a loss of weight is a measure of caloric deficiency and not necessarily a measure of the possible deficiency of other essential nutrient factors. Although it is

true that deficiency of essential nutrients is more likely to occur where there is loss of weight, on the other hand, the qualitative aspects of the diet of those persons with no loss of weight and low total serum proteins require close evaluation before one can be certain that the low serum protein is entirely on the basis of hepatic insufficiency

The level of the serum albumin fraction which is generally considered a more accurate measure of hepatic function than that of total serum protein is indicated in figure 2. If one considers values of 3 Gm per hundred cubic centimeters or higher as within the normal range, it will be observed that in 27 of the 63 cases there is an abnormally low value. In no instance was there evidence of renal damage and as in the case of total serum proteins there was no correlation between the degree of loss of weight and the level of serum albumin. Hence, it appears at least

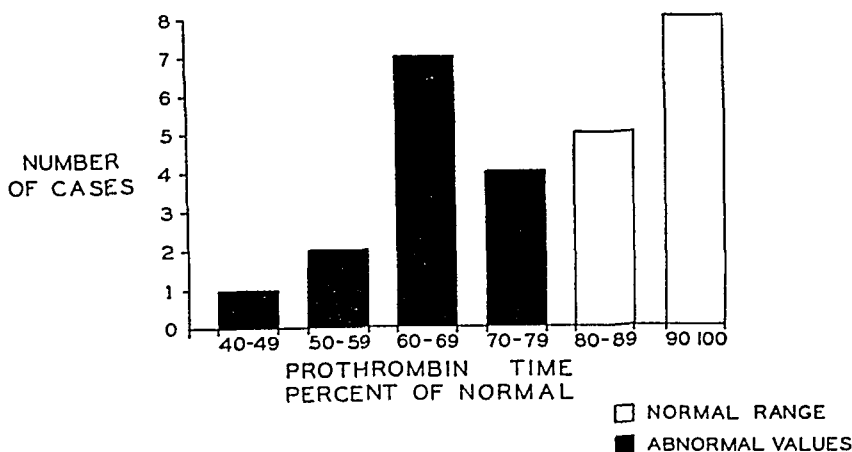


Fig. 3—Prothrombin time in cases of chronic idiopathic ulcerative colitis

suggestive that as reflected by the level of serum albumin, 43 per cent of our cases of chronic ulcerative colitis gave evidence of hepatic insufficiency.

Prothrombin Time—The occurrence of prolonged prothrombin time has been frequently observed in chronic ulcerative colitis¹⁰. Thus, Page and Bercovitz^{10a} found in frequent determinations of the prothrombin time in 25 cases of chronic ulcerative colitis that 28.5 per cent showed a constant hypoprothrombinemia, 61.9 per cent fluctuated between normal and abnormal and only 9.5 per cent were constantly normal.

10 (a) Stewart, J. D., and Rourke, G. M. Prothrombin and Vitamin K Therapy, *New England J Med* **221** 403, 1939. (b) Mackie, T. T. Vitamin K Deficiency in the Absence of Jaundice, *New York State J Med* **50** 987, 1940. (c) Butt, H. R., and Snell, A. M. Vitamin K, Philadelphia, W. B. Saunders Company, 1941. (d) Page, R. C., and Bercovitz, Z. Prothrombin and Fibrinogen Studies in Chronic Ulcerative Colitis, *Am J Digest Dis* **9** 419, 1942.

In our cases prothrombin time was determined in 27 cases. The levels for all cases expressed as per cent of normal prothrombin time are shown in figure 3. We accepted values of 80 per cent of normal time or more as being normal. Under such circumstances, 14 cases (51 per

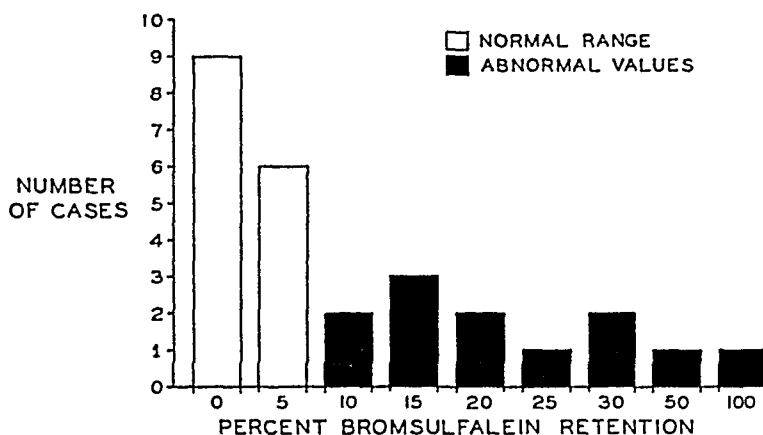


Fig 4—Results of bromsulfalein test in cases of chronic idiopathic ulcerative colitis

cent) revealed abnormally low levels. The low level of the prothrombin in itself could not necessarily be accepted as an indication of hepatic insufficiency, but could be readily interpreted, as previously suggested,^{10b} as a manifestation of deficient intake or absorption of vitamin K. How-

TABLE 2—Results of Cephalin Cholesterol Flocculation Test in 12 Cases of Chronic Ulcerative Colitis

Case	Duration (Months)	Loss of Weight (pounds)	Cephalin Flocculation	
			24 Hours	48 Hours
1	24	0	++	++++
2	24	0	0	0
3	48	0	++	++++
4	18	10	0	++
5	24	12	0	+
6	1	15	0	0
7	15	20	0	0
8	4	22	+	++++
9	12	27	0	0
10	5	31	0	0
11	5	35	++	++++
12	24	40	++	++++

ever, our data are more significant as an indicator of hepatic insufficiency in view of the fact that all prothrombin values indicated were determined after administration of adequate daily supplementary vitamin K, generally supplied parenterally.

Bromsulfalein Test—The bromsulfalein dye retention test was carried out in 27 cases. In all instances 5 mg of dye per kilogram of body weight was administered intravenously and the degree of dye retention determined at the end of forty-five minutes. Retention of 10 per cent or more of the dye was considered abnormal. Employing this criterion, 12 (44 per cent) of our 27 cases revealed evidence of hepatic insufficiency (fig 4). In view of the fact that it has been suggested that any degree of retention of dye is indicative of hepatic disease, it may be of significance that in 6 additional cases there was a retention of 5 per cent of the dye at the end of forty-five minutes.

TABLE 3—*Comparison of Various Tests of Liver Function in 21 Cases of Chronic Idiopathic Ulcerative Colitis**

Case	B S P	Cephalin Cholesterol	Prothrombin Time	Total Serum Protein
1	+	+	+	+
2	—	—	+	—
3	+	+	—	+
4	+	+	—	—
5	+	+	—	+
6	—	—	—	—
7	—	—	—	—
8	—	—	—	—
9	—	+	+	+
10	—	—	—	+
11	—	—	+	—
12	—	—	+	—
13	—	—	—	—
14	—	—	—	—
15	—	—	—	—
16	—	—	+	+
17	+	—	—	+
18	+	—	+	+
19	+	+	—	—
20	—	—	—	—
21	—	—	—	+

*Normal — abnormal +

Cephalin-Cholesterol Flocculation Test—Table 2 indicates the results

obtained from the use of this test in 12 cases of chronic ulcerative colitis. Following the suggestion of Mateer¹¹ the test was considered to be positive, that is indicative of active parenchymal disease of the liver, only if there was at least a two plus reaction at the end of forty-eight hours. Six (50 per cent) of the 12 cases of ulcerative colitis revealed damage of the liver as reflected by this test. An attempt was made to determine whether there was any relationship between either the duration of the ulcerative colitis or the degree of malnutrition as indicated by the loss of weight and the presence of hepatic insufficiency as reflected by this

11 Mateer, J. G., Baltz, J. I., Marion, D. F., and MacMillan, J. M. Liver Function Test, J. A. M. A. 121: 723 (March 6) 1943.

test As indicated in table 2 there is no relationship with either of these two factors For example, there are positive and negative results of tests in cases of short duration (compare cases 10 and 11) and also in cases of long duration (compare cases 5 and 12) Likewise, there are positive and negative reactions both where there is no loss of weight (cases 1 and 2) and where there is marked loss (cases 10 and 12)

Comparison of Various Tests of Function of the Liver—In view of the fact that the four function tests employed were often carried out on different patients, there is rather good agreement in the results as far as they indicated the percentage of patients with chronic ulcerative colitis who have hepatic insufficiency Thus, in the tests employed abnormality was revealed as follows serum albumin, 43 per cent, prothrombin time, 51 per cent, bromsulfalein, 44 per cent, and cephalin-cholesterol flocculation, 50 per cent However, a more accurate comparison of the results of these tests can be obtained by evaluating them in those instances in which two or more tests were carried out in the same patient at the same time This was true in 21 cases Using the criteria already described for abnormal tests, we compared in table 3 all tests carried out in the same patient It will be noted that in all instances in which both the bromsulfalein and the cephalin-cholesterol flocculation tests were carried out there is agreement as to the presence or absence of hepatic insufficiency The prothrombin time agrees with the results of the bromsulfalein and cephalin-cholesterol flocculation test in 4 instances and is at variance with these tests in 4 instances Likewise, the total serum proteins are in agreement with the dye and flocculation tests in 3 instances but at variance in 4 instances The prothrombin time and total serum proteins are generally in agreement with each other as tests in evaluating hepatic function It thus appears that the bromsulfalein and flocculation tests best reflect the functional capacity of the liver in ulcerative colitis, with the level of the total serum proteins and the prothrombin time being of less value

Definite Instances of Hepatic Cirrhosis—As previously indicated, 10 definite instances of hepatic cirrhosis associated with chronic ulcerative colitis have been reported in the literature¹² In our material 4 cases revealed definite evidence of hepatic cirrhosis in association with chronic ulcerative colitis Because such instances have been reported so uncommonly, a brief summary of each case is presented

CASE 1—W B (case 17, table 6), a 20 year old woman, was admitted to the University Hospital on March 8, 1943, with the history of persistent mucous and bloody diarrhea of ten to fifteen stools daily since March 1938 This diarrhea had persisted in spite of various types of oral and parenteral therapy It had been unassociated with fever, anorexia, nausea or loss of weight Abdominal cramping had been present intermittently since the onset of diarrhea For one year prior

¹² Logan⁵ Comfort and others^{9a} Tumen and others^{9b}

to admission there had been mild tenderness in the right lower quadrant. There was no history of infectious jaundice or of the ingestion of hepatotoxic drugs. The past history was not significant. On admission physical examination revealed a well nourished woman (weight, 138 pounds [62.6 Kg], height 64 inches [162.56 cm]) who did not appear ill. Aside from generalized abdominal tenderness and hepatic enlargement (3 cm below the right costal margin) the examination gave negative results. There was sigmoidoscopic and roentgen evidence of chronic ulcerative colitis. Cultures of the stools did not reveal pathogenic organisms, and the examinations for parasites all gave negative results. There was a moderate hypochromic anemia (hemoglobin 9.8 Gm per hundred cubic centimeters). The patient was given succinylsulfathiazole, a high protein, soft fiber diet, iron and supplementary vitamins. She improved promptly, and by the time of discharge (April 26, 1943) the stools were one to two daily and formed. Her weight was 141 pounds (64 Kg). After discharge she did well until October 1943. At this time the stools increased to five to six daily, and there was undue fatigue. This continued, but was associated with a gain in weight to 150 pounds (68 Kg). She was readmitted on Feb. 21, 1944. Physical examination now revealed a pale, chronically ill woman.

TABLE 4—Summary of Results of Liver Function Tests in Case 1

Date	Pro-thrombin*	Cephalin† Flocculation	Blood Bilirubin (mg %)	Hippuric Acid‡	Galactose Tolerance#	Serum Proteins			
						Total	Alb	Glob	A/G
2-24-44						8.9	4.3	4.6	0.9
3-25-44	65								
4- 4-44	57	++++	2.0	0.55					
4-10-44	66		2.0			7.8	2.6	5.5	0.5
4-28-44	65		3.8						
5- 2-44	58		7.0						
5- 8-44	72								
5-18-44	61				3.69				
5-24-44	57		2.5			8.1	3.4	4.7	0.8
5-31-44	50								
6-12-44	62	++++	6.0	0.70	3.1	6.1	1.9	4.2	0.5
6-29-44	55		6.0						
7-13-44	46								

*Per cent of normal †Forty-eight hour reading ‡Intravenous test gave normal results 1 Gm or more excreted in one hour #Oral test gave normal results 3 Gm or less excreted in five hours

There were ascites and generalized peripheral edema. The therapeutic program of the first admission was reinstated. There was slight improvement with a decrease of the stools to three to four daily. Icterus was first observed on March 25, 1944. After this her condition deteriorated rapidly and in spite of intensive therapy, including a protective liver diet, the patient became worse and died on July 19, 1944. The results of the tests of liver function which were carried out are summarized in table 4. It should be noted that the prothrombin time was obtained in spite of massive amounts of parenterally administered vitamin K. Autopsy revealed chronic ulcerative colitis and toxic parenchymatous hepatitis in both subacute and healed stages.

Comment This is a clearcut case of severe hepatic disease in association with chronic ulcerative colitis. The evidence appeared to indicate clearly that the hepatic disease had its onset subsequent to the colitis and seemed to become manifest and progressive simultaneously with an exacerbation of the colonic disease.

CASE 2—E Q (case 16, table 6), a 24 year old man, was admitted to the University Hospital on Aug. 22, 1944, with the complaints of diarrhea and weakness. Diarrhea had begun in March 1939, following acute infection of the upper

respiratory tract Stools had varied in number from five to ten daily and had frequently contained small amounts of fresh blood Various sulfonamide compounds and a bland diet had had little influence on the diarrhea The weight had varied from 126 to 135 pounds (57.2 to 61.2 Kg), but during the last few weeks prior to admission it had increased to 145 pounds (65.8 Kg) His appetite had remained excellent There had been two recent short febrile episodes with a temperature up to 101 F Until two months prior to admission there had been no abdominal pain but at that time a dull ache developed in the right flank and persisted until admission Associated with the pain the patient had noted a gradual increase in the size of the abdomen During the same period there was a questionable history of the presence of jaundice The stools had varied from yellow to dark brown and the urine had occasionally been dark Aside from the occurrence of nonseasonal hay fever since childhood the past history was irrelevant There was no history of the ingestion of hepatotoxic drugs or any history suggestive of infectious hepatitis Physical examination on admission revealed a malnourished man There was no fever The skin was pasty and pale, but not icteric The nasal mucosa was boggy and edematous There were definite ascites and slight peripheral edema Roentgen studies of the gastrointestinal tract on Aug 24, 1944, were reported on as follows "Probable widespread segmental inflammatory disease of the small bowel, colon and rectum, nonfunctioning gallbladder, hepatomegaly, ascites" Results of laboratory studies are given in table 5

TABLE 5—*Results of Laboratory Studies in Case 2*

Date	Hemoglobin	Blood	Prothrombin	Serum Proteins		
	(Gm/100 Cc)	Bilirubin	(% of Normal)	Total	Albumin	Globulin
8/22/44	26	0.9	40	7.2		
8/29/44	5.9	17.5	40	6.4	2.2	4.2
9/6/44	8.9	20.0				

Daily small transfusions were immediately started, and he was given a high protein soft fiber diet, large amounts of vitamin K parenterally and succinyl-sulfathiazole From the onset the stools were tarry and liquid Jaundice was first observed on the fourth day in the hospital His condition deteriorated, and it was not possible to maintain his hemoglobin because of continuous loss of blood by rectum For these reasons, an ileostomy was performed on the seventh day in the hospital The patient tolerated the operation well and gradually improved However, the ascites gradually reaccumulated and on the nineteenth day in the hospital he had a massive hematemesis and died The autopsy revealed extensive chronic ulcerative colitis, chronic acute yellow atrophy of the liver (fig 5) and ruptured esophageal varices

Comment This, also, is a clearcut case of severe disease of the liver associated with ulcerative colitis The loss of blood that terminated the picture was incorrectly presumed to be due to bleeding from the colon but actually was due to bleeding from esophageal varices consequent on the hepatic disease In this case again, the hepatic disease apparently had its onset subsequent to the ulcerative colitis

CASE 3—B W, a 21 year old woman, had been well until December 1943, at which time, after an acute infection of the upper respiratory tract, she began to have chronic fatigue and severe chronic constipation Enemas and cathartics were resorted to for relief, but shortly thereafter there was the onset of diarrhea characterized by the passage of five to ten bloody stools daily This was accompanied by severe abdominal cramping She was hospitalized in her local hospital and

improved under medical therapy, with the stools diminishing to one to two daily. In May 1944 there was a recurrence of all her original symptoms. Her past history revealed that in the winter of 1941 the patient had "catarrhal jaundice," with jaundice persisting for three months. There was also an episode of jaundice in January 1943, which lasted about two weeks. She was first admitted to the University Hospital on July 25, 1944. Examination at this time showed a chronically ill but well nourished woman (weight 144 pounds [65.3 Kg], height 62 inches [157.48 cm]). Her temperature was 99.2°F. There was tenderness in the right lower abdominal quadrant, but the physical examination otherwise gave normal results. The hemoglobin value was 6.2 Gm per hundred cubic centimeters. Roentgenograms revealed evidence of widespread inflammatory disease of the small bowel and colon. The sigmoidoscopic picture was characteristic of chronic ulcerative colitis. Results of cultures of the stools were all within normal limits.

TABLE 6—*Summary of Results of Liver Function Tests in Case 3*

Date	B S P *	Cephalin Flocculation		Serum Proteins				Pro-throm-bin†	Hippuric Acid‡
		24	48	Total	Alb	Glob	A/G		
1-6-44				6.8	3.6	3.2	1.1		
7-25-44									
1-9-45	100			8.0	4.0	4.0	1.0		0.8
1-16-45	90								
5-14-45	25								0.9
11-15-45	90			7.3	3.3	4.0	0.82		
12-1-45		++++	++++						
5-14-46	40	++++	++++						
8-8-46				8.8	4.2	4.6	0.92		
8-15-46		++++	++++	8.2	4.0	4.2	0.95		
9-13-46				9.8	4.6	5.2	0.99		
10-12-46				9.0	4.2	4.8	0.87	80	
3-10-47	100	++++	++++	9.2	4.6	4.6	1.0		
5-8-47		++	++++						

*50 mg per kilogram readings at forty-five minutes
 †Per cent of normal
 ‡Intravenous test normal 1 Gm or more excreted in one hour

Chemotherapy, rest in bed and high protein, low fiber diet resulted in prompt symptomatic relief. Since the original admission, this patient has been seen at frequent intervals. Up to the present time there have been two severe recurrences, but during the last year the patient had not had diarrhea, worked daily and her weight was 170 pounds (77.1 Kg). In January 1945 the liver was first found to be palpable about 5 cm below the right costal margin. It was hard in consistency but not nodular. There was definite splenomegaly. There had been three episodes of edema of the face and ankles. Since January 1946 the patient had been given a high protein diet, choline and phthalylsulfathiazole. For the last year she had done well, having a definite remission of colitis. The results of the tests of liver function carried out in this patient are summarized in table 6.

Comment. In contrast to the previous 2 cases, in this instance there is definite evidence that the serious disease of the liver apparently had its onset prior to the

ulcerative colitis The history of "catarrhal jaundice" in 1941, with a possible recurrence of jaundice in January 1943, is highly suggestive that in this instance we were dealing with chronic hepatitis or hepatic cirrhosis occurring as the end result of an infectious hepatitis One can only speculate as to the influence of the severe colitis either in adding further damage to an already diseased liver or in influencing the progression of the chronic hepatitis

CASE 4—F M, a 46 year old man, was well until March 1942 At that time severe headaches, dyspnea and cardiac failure developed Severe hypertension was discovered by his family physician Symptoms of cardiac failure persisted, and for

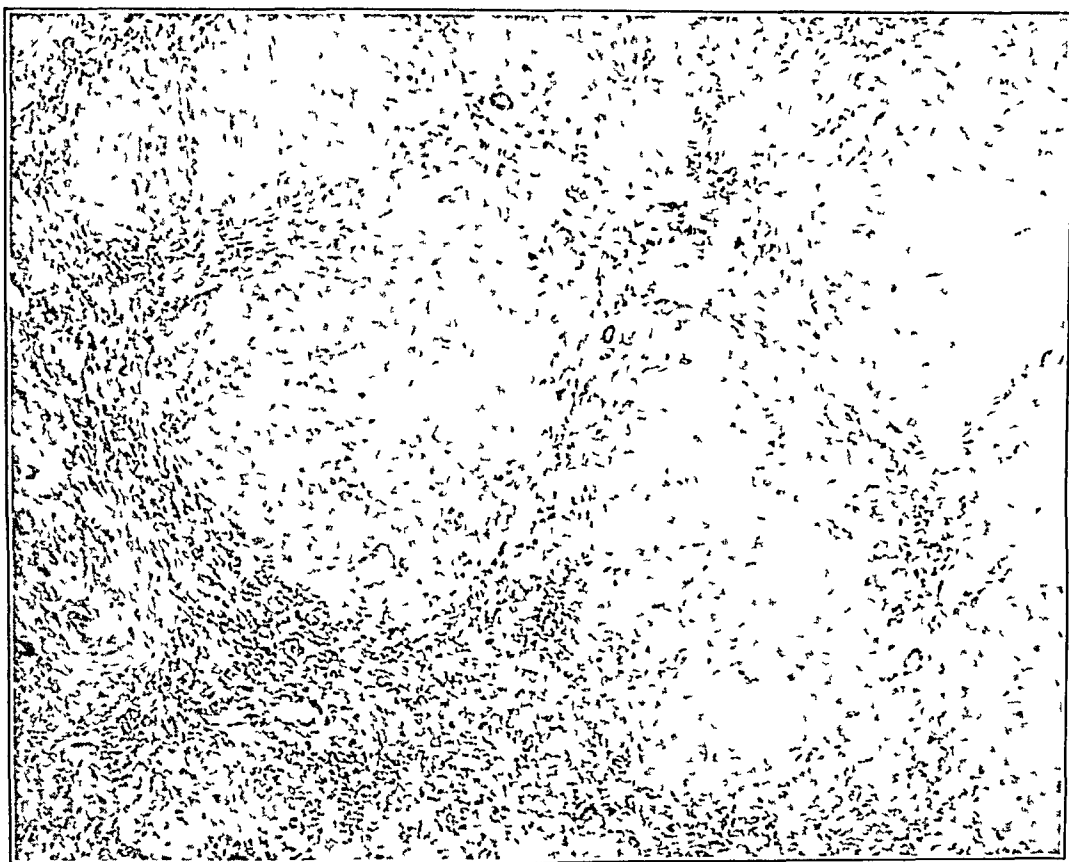


Fig 5—Low power view of liver in a case of chronic ulcerative colitis (E I, case 16, table 6) This was interpreted as "chronic acute yellow atrophy"

this reason the patient was first admitted to the University Hospital on July 8, 1943 At this time examination revealed, in addition to other signs of cardiac failure, marked ascites and hepatomegaly The patient responded well to digitalis, diuretic drugs and rest in bed He was discharged on Aug 15, 1943 He remained well until June 1944, when cardiac failure recurred This persisted in a chronic form until he was readmitted to the University Hospital on Jan 25, 1945 At this time there were marked cardiomegaly, hepatomegaly and splenomegaly, as well as ascites Treatment with digitalis and diuretic drugs resulted in cardiac compensation, and because of persistent hypertension, a bilateral supradiaphragmatic resection of the splanchnic nerve was carried out Postoperatively the blood pressure became normal and remained at this level until time of discharge on April 25, 1944

The patient had no further cardiac difficulties. In November 1945 he first noted gross blood in his stools. Shortly thereafter he began to have gradual increase in his stools, finally passing fifteen to twenty bloody, liquid stools daily. Associated with this there was generalized lower abdominal discomfort and marked anorexia. There was a 35 pound (15.9 Kg) loss of weight during the two months prior to his admission to the University Hospital on March 9, 1946. Physical examination at this time revealed a normal blood pressure, cardiomegaly and tenderness in both flanks. The liver and spleen were palpable. There was no ascites or peripheral edema. There was sigmoidoscopic and roentgen evidence of chronic ulcerative colitis. The hemoglobin value was 11 Gm per hundred cubic centimeters. The patient's course in the hospital was stormy. The temperature rose to 101.4 F daily. The stools continued up to fifteen daily. There was persistent anorexia, and weight decreased approximately 5 more pounds (2.3 Kg). However, at no time was there evidence of cardiac failure. After six months of hospitalization the patient was improved sufficiently to be transferred to his local hospital for further care. The results of the liver function tests carried out on this patient are given in table 7.

TABLE 7—Results of Liver Function Tests in Case 4

Date	Bromsulfalein	Cephalin		Serum Proteins		
		Flocculation Test	Prothrombin Time	Total	Albumin	Globulin
2/ 1/45	50%			76	48	28
2/ 7/45	15					
3/25/46	15	4				
6/19/46				78	34	44
7/16/46	25		100			
9/ 5/46				69	35	34

Comment. In this case there was definite ulcerative colitis and definite evidence of severe hepatic disease. However, there was evidence of liver insufficiency (bromsulfalein 50 per cent on Feb. 1, 1945) prior to the onset of the ulcerative colitis. At that time it was felt to be associated with his frequent and chronic episodes of cardiac failure. However, at the time of the occurrence of his ulcerative colitis there was no clinical evidence of cardiac failure. One is thus forced to speculate that in this case there was probably preexisting damage of the liver ("cardiac cirrhosis") and that the ulcerative colitis was a factor only in that it added further damage or caused an exacerbation or progression of the liver insufficiency.

Autopsy Findings in Chronic Ulcerative Colitis.—Autopsy findings in 17 fatal cases (including cases W. B. and E. Q.) of chronic ulcerative colitis were studied. Special emphasis was placed on the histologic changes in the liver. The essential data in these cases are tabulated in table 8. It will be noted that there were 10 female and 7 male patients in this series. The age varied from 2½ to 40 years. Symptoms had been present for one month to six years. In all cases there had been an appreciable loss of weight. Histologically there were definite abnormali-

ties of the liver parenchyma in all but 1 case (case 1) In 2 cases¹³ there were definite changes characteristic of cirrhosis In all other cases there was either fatty infiltration or degenerative fatty infiltration or both Degenerative fatty infiltration is widely accepted as evidence of the functional impairment of the hepatic cells to handle lipids normally It is considered early evidence of hepatic insufficiency If we exclude case 1 and all other cases in which only simple fatty infiltration was present, we

TABLE 8—*Summary of Findings in 17 Autopsied Cases of Chronic Idiopathic Ulcerative Colitis*

Case	Sex	Age	Duration of Symptoms (Months)	Loss of Weight (Pounds)	Hepatic Pathologic Process
1	F	31	60	35	Acute exacerbation chronic passive congestion, no lipoidosis
2	F	34	2	30	Marked fatty infiltration
3	M	17	4	17	Fatty infiltration, cloudy swelling simple atrophy
4	M	2½	1	?	Marked degenerative fatty infiltration, cloudy swelling
5	M	37	9	27	Patchy fatty infiltration, acute exacerbation chronic passive congestion
6	M	39	36	85	Marked lipoidosis simple atrophy, cloudy swelling, acute passive congestion
7	F	17	7	16	Marked fatty and degenerative fatty infiltration, cloudy swelling
8	F	24	12	54	Extreme fatty infiltration and slight degenerative fatty infiltration
9	M	15	37	21	Marked fatty infiltration, cloudy swelling, simple atrophy
10	M	40	30	43	Peripheral degenerative fatty infiltration
11	F	17	3	14	Fatty infiltration peripheral portion of lobules, cloudy swelling
12	F	37	1½	31	Advanced fatty infiltration, focal excessive vacuolar change in parenchyma
13	F	29	1½	?	Marked fatty infiltration, slight degenerative fatty infiltration moderate lymphocytic infiltration in triads
14	F	27	5	?	Marked degenerative fatty infiltration, increase in lymphocytes in trinites
15	F	17	4	26	Very marked fatty infiltration, increased wandering cells in portal canal
16	M	24	60	10	Chronic acute yellow atrophy
17	F	20	72	10	Toxic parenchymatous hepatitis in subacute and healed stages

find that 11 of our 17 cases show definite evidence of damage to the liver It will be recalled that these figures correspond closely with those of Logan⁵

COMMENT

The occurrence of hepatic insufficiency in approximately 50 per cent of our cases of ulcerative colitis and the occasional occurrence of frank

cirrhosis does not appear to be a fortuitous association. In an occasional case (e.g., cases 3 and 4) in which the onset of the cirrhosis occurred prior to that of ulcerative colitis the hepatic insufficiency probably cannot be related fundamentally to the intestinal disease. However, in the vast majority of our cases the evidence seems to indicate that the hepatic insufficiency is fundamentally and etiologically related to the occurrence of ulcerative colitis. The following facts support this point of view:

- 1 The hepatic insufficiency developed after the onset of the colitis.
- 2 Hepatic insufficiency of such severity as to lead to cirrhosis is at least twice as common in males as in females.¹⁴ Ulcerative colitis is equally common in both sexes.¹⁵
- 3 Cirrhosis is most common above the age of 40,¹⁴ while ulcerative colitis is most common below that age.¹⁵

Studies of the hepatic histology at necropsy indicate in both our series and that of Logan⁵ that fatty changes in the liver are common in ulcerative colitis. This fatty change, while it may vary in severity and degree, appears to be the basis for the hepatic insufficiency that is reflected in diminished function of the liver as detected by clinical and laboratory means. Once fatty infiltration is present, the possibility that more severe insufficiency and finally frank hepatic cirrhosis may develop has been demonstrated conclusively, both in animals¹⁶ and in man.¹⁷ The only point to be considered further is the origin of the fatty changes in the liver in ulcerative colitis. We believe there are two main factors: the severe malnutrition and the toxemia that are present in the disease. Both of these conditions occurring in many diseases are known to produce fatty infiltration of the liver.¹⁸ The situation in tuberculosis, particularly, when there is severe malnutrition and toxemia, is entirely analogous to ulcerative colitis.¹⁹

14 Ratnoff, O. D., and Patek, A. J., Jr. *The Natural History of Cirrhosis of the Liver*, *Medicine* **21**: 207, 1942.

15 Willard, S. H., Pessel, J. F., Hundley, J. W., and Bockus, H. L. *Prognosis of Ulcerative Colitis*, *J. A. M. A.* **111**: 2078 (Dec. 3) 1938.

16 Chaikoff, I. L., Cannon, C. L., and Biskind, G. R. *Fatty Infiltration and Cirrhosis of the Liver in the Depancreatized Dog Maintained with Insulin*, *Am. J. Path.* **14**: 101, 1938.

17 Connor, C. L. *The Etiology and Pathogenesis of Alcoholic Cirrhosis of the Liver*, *J. A. M. A.* **112**: 387 (Feb. 4) 1939.

18 Mottram, V. H. *Fatty Infiltration of Liver in Hunger*, *J. Physiol.* **33**: 281, 1909. Ralli, E. P., Paley, H., and Rubin, S. H. *Liver Lipids and Their Distribution in Disease. Analysis of Sixty Human Livers*, *J. Clin. Investigation* **20**: 413, 1941.

19 Jones, J. M., and Peck, W. M. *Incidence of Fatty Liver in Tuberculosis with Special Reference to Tuberculous Enteritis*, *Arch. Int. Med.* **74**: 371 (Nov.) 1944. Hurst, A., Maier, H. M., and Lough, S. A. *Studies of Hepatic Function in Pulmonary Tuberculosis*, *Am. J. M. Sc.* **214**: 431, 1947.

Our concept of the development of hepatic insufficiency in ulcerative colitis is that as a result of malnutrition, toxemia or both, fatty changes occur in the liver. These fatty changes may be of sufficient degree to give rise to hepatic insufficiency of such slight degree that it can be detected only by tests of liver function, or it may progress to definite cirrhosis. Because the onset of the liver insufficiency is that of a fatty change, early in its course, it is reversible and is probably amenable to the influence of lipotropic substances. In our data we attempted to correlate loss of weight as a measure of malnutrition with the occurrence of liver insufficiency. No correlation could be detected. However, since loss of weight is no accurate measure of nutritional deficiency, this cannot be considered a serious objection to our concept of the development of hepatic insufficiency. Moderate or no loss of weight may occur in the presence of specific nutritional deficiencies (protein, choline, and so forth), and the converse may likewise, be true.

SUMMARY AND CONCLUSIONS

Study of hepatic function in patients with chronic idiopathic ulcerative colitis by means of the bromsulfalein test, cephalin-cholesterol flocculation test, prothrombin time and serum protein revealed the presence of hepatic insufficiency in approximately 50 per cent of the 70 cases investigated.

The bromsulfalein and cephalin-cholesterol flocculation tests appeared the most satisfactory indicators of hepatic insufficiency.

In 11 of 17 cases of chronic ulcerative colitis studied post mortem, there was histologic evidence of a hepatic pathologic process. Degenerative fatty infiltration was most common, but definite cirrhosis was present in 2 instances.

Four cases of cirrhosis of the liver associated with chronic ulcerative colitis are reported. In 2 instances the cirrhosis had its onset prior to the colitis and was probably not related etiologically to the latter. In the other 2 cases the cirrhosis had its onset after the colitis.

Evidence is presented to indicate that hepatic insufficiency in association with ulcerative colitis probably has its origin in fatty changes in the liver that occur as a consequence of severe malnutrition or toxemia or both.

STUDY OF TREMOR IN SOLDIERS

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THE CLINICAL study of tremors has been the subject of a great deal of investigation. Tremors occur in a wide variety of conditions. Most observations, however, have been confined to disease states such as Parkinson's disease and multiple sclerosis. In such conditions as thyrotoxicosis, alcoholism and anxiety states a tremor of the outstretched fingers is considered an important, if not a cardinal, clinical sign. That a tremor can also occur in normal persons has long been known but generally overlooked. "My flesh trembleth for fear of the Lord," a quotation taken from the Bible,¹ illustrates the antiquity of this observation.

In the course of a study of palmar sweating among soldiers at an army general hospital, it was found that soldiers with an excessive palmar sweat response frequently exhibited pronounced tremors. A study was therefore undertaken to investigate and correlate these phenomena. To study the sweat response, the technic of Silverman and Powell² was used. In this technic a sweat pattern of the finger tips is portrayed on chemically treated paper. Prints are obtained which vary in intensity according to the amount of sweating. A response was considered intense when a black, blotchy stain was produced (fig 1). To record the tremors, a modification of an apparatus described by Morris³ was used. An ordinary 6 inch (15 cm) loud-speaker was enclosed, except for its opening, in a rigid wooden cabinet. The opening of the speaker was sealed over with a tight rubber diaphragm, being thus converted into an air-tight chamber (fig 2). The wooden cabinet was of sufficient length and width to provide a comfortable base for the upper extremity, and the hand was permitted to rest on the rubber diaphragm. With this arrangement the vibrations of the fingers were transmitted through the loud-speaker and converted into electrical energy. The latter was finally picked up and recorded with an ordinary electrocardiograph machine (General Electric and Sanborn models were both used). Each patient was seated comfortably in a quiet room, free from distracting influences. With experience, it was learned that better

1 Psalms 119:120

2 Silverman, J. J., and Powell, V. E. Studies on Palmar Sweating. I. A Technique for the Study of Palmar Sweating, *Am J M Sc* **208**:297, 1944

3 Morris, A. A., Jr. An Apparatus to be Used in Recording Tremors, *Arch Neurol & Psychiat* **49**:123 (Jan) 1943

results were obtained when the hand was placed in contact with the diaphragm in such a way that the thenar, hypothenar and tips of the distal phalanges made contact with its surface (fig 3)



Fig 1—Classification of sweat pattern *A* shows mild response and *B* intense response

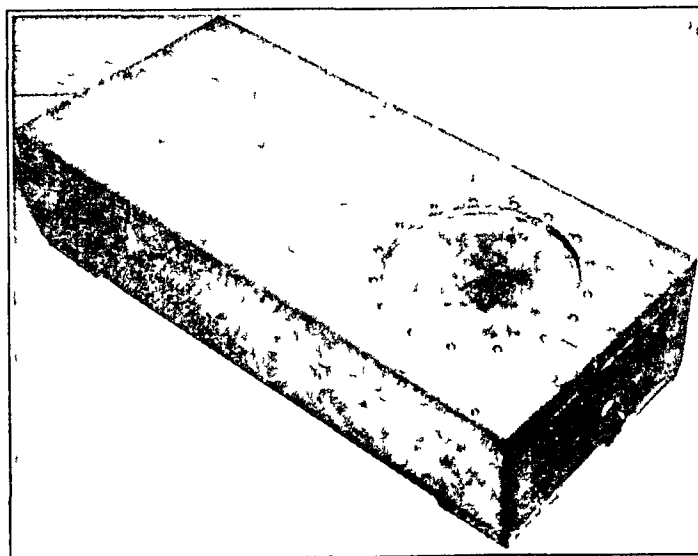


Fig 2—Loud-speaker unit, enclosed in cabinet, for transmitting tremors (United States Army Signal Corps photograph)

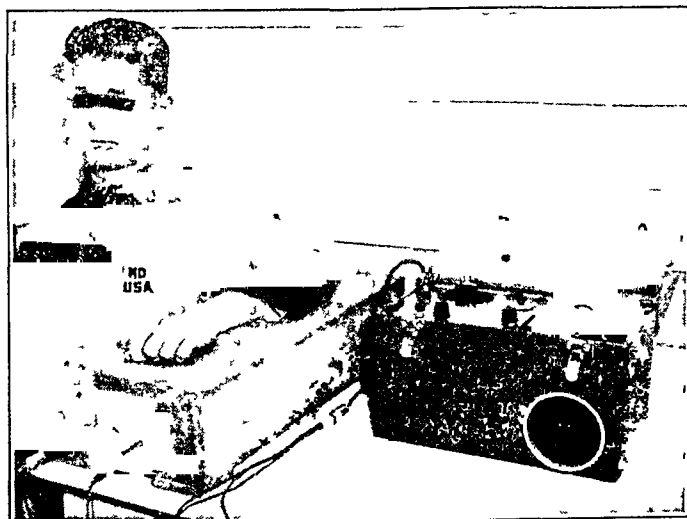


Fig 3—Patient in position for recording of a tremor The loud-speaker unit is connected with an electrocardiographic machine (United States Army Signal Corps photograph)

The tremor apparatus was found to be extremely sensitive in reproducing tremors, and a system had to be devised to standardize the results. Officers with no clinically demonstrable tremors of the fingers of the outstretched hand, confirmed by two or more competent observers, were used for calibration. Tremor records were then made for these officers, and the amplification was so adjusted that the finished record barely demonstrated oscillations of less than 1 mm (fig 4). The apparatus was kept at this amplification throughout the study. With this standardization it was found that clinically pronounced tremors always measured at least 5 or more millimeters on the graph and frequently measured

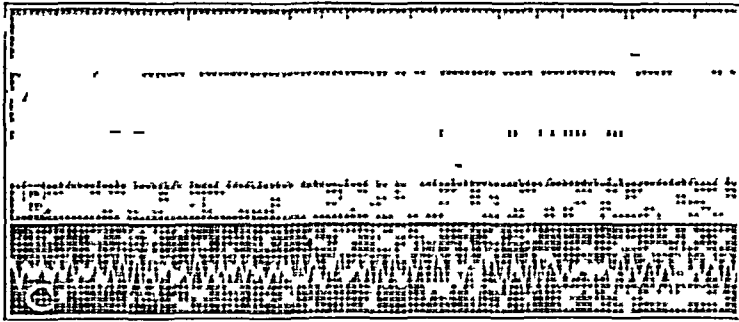


Fig 4—Classification of tremor. *A*, record of a tracing taken without a patient, *B*, example of a tremor of low amplitude, *C*, example of a tremor of pronounced amplitude.

more than 10 mm (figs 5 and 6). In classifying a tremor, measurements were taken from the peak to the trough of each wave. All tremor waves were measured and the average amplitude determined. Records measuring from 1 to 5 mm in amplitude were considered equivocal and excluded from the classification of pronounced tremor. At frequent intervals the apparatus was checked and adjusted for accuracy.

The records were obtained by trained army personnel. The tremor of one hand was recorded, and the other hand was used for the study of the palmar sweat response. No set plan was followed, but usually the tremor record was obtained first. In many cases the tremor record and the sweat pattern were obtained simultaneously. To insure accuracy, the tests were frequently repeated on the same patient. It should be emphasized that the test situation was more or less similar for all patients.

In an army hospital, and even before reaching a hospital, soldiers are subjected to all kinds of tests, and they were in most instances conditioned to a study of this nature

FINDINGS

The tremor and sweat patterns in a total of 321 persons, divided into three groups, were studied. The findings in all groups are summarized in the table

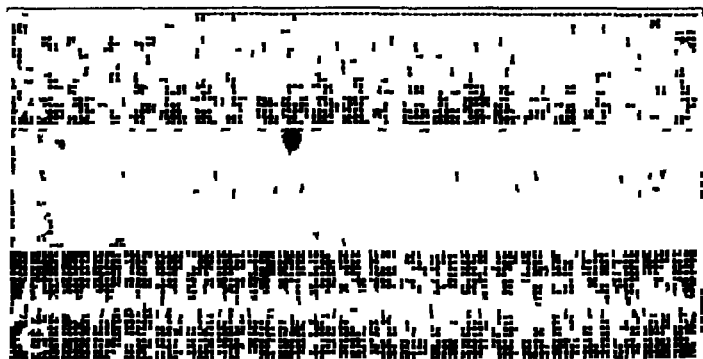


Fig 5—Examples of variations in tremor rates. In *A* the rate is 7 per second, in *B* 12 per second and in *C* 21 per second

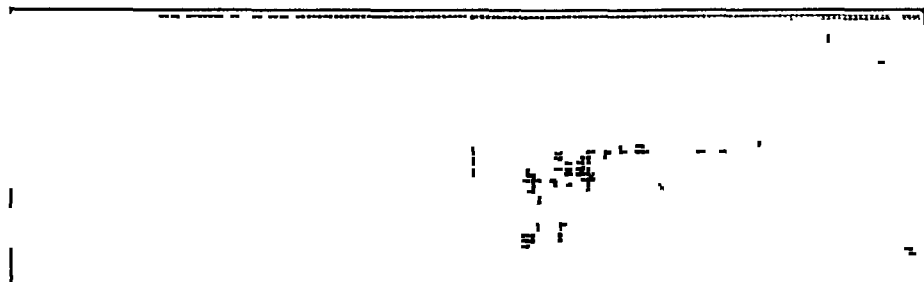


Fig 6—Illustration of the wide variety of tremor patterns. *A*, from a patient with a history of alcoholism and anxiety, *B*, from a patient in a severe anxiety state, *C*, from a patient with conversion hysteria, *D*, from a medical officer who consciously tried to produce a tremor

The first group consisted of 174 soldiers who were in the process of undergoing basic military training at an Army Infantry Replacement Center. All these soldiers were recruits, and the average age was 19 years. In this group 30 (17.2 per cent) were found to have a pronounced tremor, and 25 (14.4 per cent) demonstrated an excessive palmar sweat response. There were 6 soldiers (3.5 per cent) who demonstrated a pronounced tremor and an excessive palmar sweat response at the same time.

The second group consisted of 111 patients who were under observation in the hospital for complaints referable chiefly to the cardiovascular system. These patients were carefully examined, and all kinds of tests, such as electrocardiographic and roentgenologic studies, blood counts and urinalyses, were made. In addition, consultations with other specialists, including psychiatrists, were obtained. No patient in this group was found to have organic disease as the basis of his complaints, and the majority were finally discharged from the hospital with a diagnosis of neurocirculatory asthenia. Anxiety features predominated in these patients. In this group there were 67 (60.4 per cent) who showed a pronounced tremor and 33 (29.7 per cent) who showed an excessive palmar sweat response. In 25 (22.5 per cent) excessive sweating and a pronounced tremor were present.

The third group consisted of 36 normal persons. In a study of this nature it is difficult to classify so-called controls, for normalcy is, after all, a relative term. Nevertheless, it was decided to use medical officers, nurses and laboratory technicians of a high rating as controls. All members of this group were considered healthy and, as far as could be determined, were emotionally stable. In this control group there were only 2 (5.6 per cent) with a pronounced tremor, and not one demonstrated a pronounced tremor and excessive palmar sweating at the same time. On the other hand, there were 6 in this group with an excessive palmar sweat response.

Throughout this study there was no characteristic tremor peculiar to each group. In all groups studied the pattern was essentially irregular, and because of this irregularity it was sometimes difficult to assign an exact frequency to a particular tremor. The tremor rates varied from 7 to 21 per second, and the average was 14.2 per second (fig. 5).

COMMENT

The significance of the sweating of the palms has been taken up elsewhere⁴. It has been shown that sweating of the palms is unique and differs from general body sweating on anatomic and physiologic grounds. The palmar sweat response is one of the important indexes of the emotions. It is increased during emotional excitement.

The physiologic interpretation of tremors is complex and beyond the scope of this paper⁵. It is not sufficiently appreciated, however, that

4 Silverman, J. J., and Powell, V. E. (a) Studies on Palmar Sweating. II. The Significance of Palmar Sweating, *Am J M Sc* **208** 298, 1944. (b) Studies on Palmar Sweating. III. Palmar Sweating in an Army General Hospital, *Psychosom Med* **6** 243, 1944.

5 Morris, A. A., Jr. The Nature of Tremors, *North Carolina M J* **5** 15, 1944.

tremor, like palmar sweating, is a normal phenomenon and takes place continuously Eshner⁶ in 1897 was the first to demonstrate clearly the occurrence of a tremor in normal persons Using a modified sphygmograph, Eshner⁶ showed objectively that a tremor existed in every one of his 100 normally tested subjects In emotional crises, such as in fright and rage, Cannon⁷ has shown that the sympathetic system is overactive and tends to discharge en masse Clinically, the striking changes are similar to those produced by adrenalemia tachycardia, dilated pupils, pallor and tremor During excitement, excessive palmar sweating also takes place, and although this is a cholinergic mechanism it has been shown that the system is also stimulated during such stages⁸

A relationship of cortical activity to variations in tremors has long been known⁹ The usual cited tremor rate is 10 per second,¹⁰ which

Analysis of the Incidence of Tremors of High Amplitude and Excessive Palmar Sweating in 111 Patients and in a Group of 174 Trainees and 36 Controls

	Excessive Sweat		Pronounced Tremor		Tremor and Sweat	
	No	%	No	%	No	%
Patients (111)	33	29.7	67	60.4	25	22.5
Trainees (174)	25	14.4	30	17.2	6	3.5
Controls (36)	6	16.7	2	5.6	0	0.0

incidentally corresponds to the major potential rhythm of the electroencephalogram seen in studies of the region of the cortex of the brain anterior to the central fissure¹¹ That the cortex is not the sole controlling influence in tremors is illustrated by their appearance in such conditions as Parkinson's disease and multiple sclerosis, in which changes can be demonstrated in other areas of the brain

Tremors vary widely in rate, amplitude and pattern Attempts to classify tremors on the basis of these variations, however, have met with little clinical success A tremor has been likened to auricular fibrillation, i.e., an irregular irregularity The lack of standardization of the technics in recording tremors has further complicated the problem of classification and accounts for many of the conflicting reports

6 Eshner, A. A. A Graphic Study of Tremor, *J. Exper. Med.* 2:301, 1897

7 Cannon, W. B. Bodily Changes in Pain, Hunger, Fear and Rage. An Account of Recent Researches into the Function of Emotional Excitement, New York, D. Appleton & Company, 1929

8 Gellhorn, E. Autonomic Regulations. Their Significance for Physiology, Psychology and Neuropsychiatry, New York, Interscience Publishers, Inc., 1943

9 Fulton, J. F. Physiology of the Nervous System, New York, Oxford University Press, 1938

10 Young, J. C. A Study of Tremor in Normal Subjects, *J. Exper. Psychol.* 16:644, 1933

11 Jasper, H. H., and Andrews, H. L. Brain Potentials and Voluntary Muscle Activity in Man, *J. Neurophysiol.* 1:87, 1938

appearing in the literature¹² Using a sensitive oscillograph, Travis and Hunter¹³ recorded a tremor frequency close to 200 per second Figure 5 demonstrates the wide variation of rate and pattern of tremors found in our study, and, as shown, rates varying from 7 to 21 per second

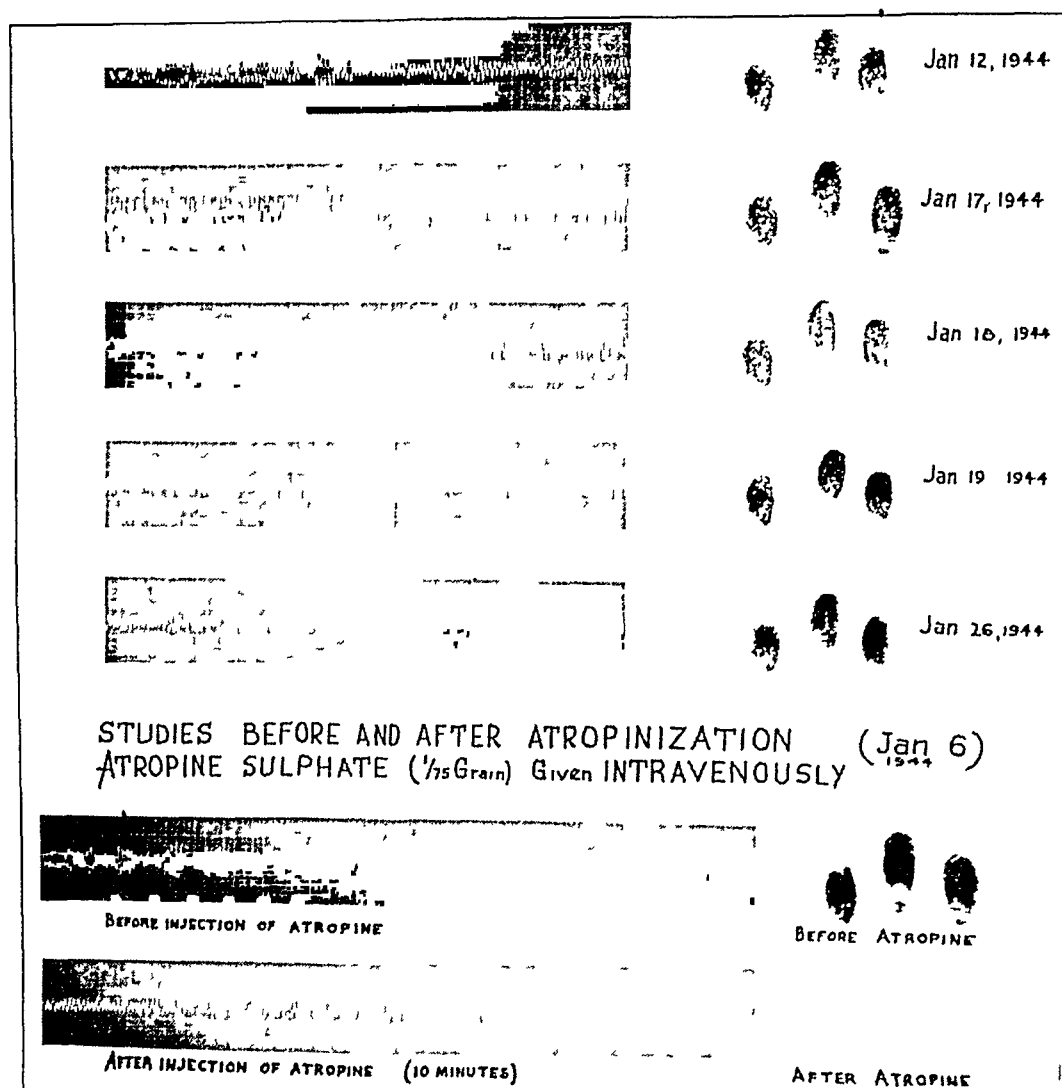


Fig 7—Study of tremor and palmar sweat response in a soldier suffering from severe neurocirculatory asthenia. Note the diminution in amplitude after the administration of atropine.

were observed. The amplitude of a tremor, on the other hand, would seem to have more clinical significance¹⁴ As Young¹⁰ pointed out, when

¹² Sollenberger, R. T. Tremor During Postural Contraction, *J. Exper. Psychol.* **21** 579, 1937.

¹³ Travis, L. E., and Hunter, T. A. Tremor Frequencies, *J. Gen. Psychol.* **5** 255, 1931.

¹⁴ French, J. W. A Comparison of Finger Tremor with the Galvanic Skin Reflex and Pulse, *J. Exper. Psychol.* **34** 494, 1944. Graham, J. D. Static Tremor in Anxiety States, *J. Neurol. & Psychiat.* **8** 57, 1945.

a tremor is modified as a result of emotional influences, the variation will be largely with respect to the amplitude and hardly at all with respect to the rate. In the course of our studies an interesting experiment was conducted which bears out this observation. A 29 year old corporal with an established diagnosis of severe neurocirculatory asthenia was studied daily for tremor and sweat records. It was known that belladonna had a quieting effect on the patient, and one morning atropine sulfate (0.87 mg.) was administered intravenously. Sample records are shown in figure 7. It was found that throughout the study of this patient the rate of the tremor (11 per second) was remarkably constant, the amplitude, on the other hand, showed definite variations. After the administration of atropine sulfate, the amplitude of the tremor, as well as the sweat response, was strikingly reduced. In many records of other patients, it was surprising to find how constant the rate was regardless of the state of tension.

In our study of various groups of army personnel, the relative incidence of tremors of large amplitude was shown. A pronounced type of tremor was found in all groups, and, confirming a well known clinical impression, the highest percentage of these tremors was found among soldiers with anxiety features. Almost two thirds of the patients with the syndrome of so-called neurocirculatory asthenia demonstrated a pronounced tremor. A similar type of tremor was also found among the recruits but not as frequently. In the control group, made up mostly of selected army personnel, a pronounced tremor, though demonstrable, was decidedly uncommon. It would seem therefore, in a general way, that a tremor of large amplitude offers some diagnostic information.

A study of the incidence of pronounced tremors associated with excessive palmar sweating in the same patient was definitely more revealing. It was found, for example, that close to one fourth of the soldiers suffering from neurocirculatory asthenia showed both excessive palmar sweating and a significant tremor, whereas among the recruits less than 4 per cent were in this category and among the controls there was not one who demonstrated both an excessive palmar sweat pattern and a significant tremor. It would seem from this study, therefore, that the association of excessive palmar sweating and notable tremors in the same person takes on more diagnostic significance than the evaluation of each finding separately.

Except for certain neurologic disorders, a tremor by itself has little diagnostic significance. As stated previously, a tremor is a normal phenomenon, easily modified by outside influences. The tremor of alcoholism cannot be distinguished from the tremor of fear or cold. There is no characteristic tremor in hyperthyroidism.¹⁵ The distinction between a fine and a gross tremor is merely one of amplitude, one easily

merges into the other, depending on the state of tension. Similarly, the distinction between a rapid and a slow tremor cannot always be made. In our experience, it was extremely difficult to predict, on clinical grounds, the rate of a tremor. Nevertheless, statements can still be found in textbooks¹⁶ assigning a tremor of a certain rate to a specific disorder.

A tremor takes on significance only when it is correlated with other signs, particularly those related to the autonomic nervous system. Its association with excessive palmar sweating, for example, is a striking feature of an anxiety state. In our study, this combination was seen almost exclusively in patients suffering from neurocirculatory asthenia, a condition now considered to be part of an anxiety state with emphasis on the cardiovascular system.¹⁷ This observation of excessive palmar sweating associated with tremors of large amplitude is not new and has been commented on as a feature of the neuroses met in wartime.¹⁸ It is hazardous to establish a diagnosis on the basis of a tremor alone. A volitional or hysterical type of tremor may closely resemble an anxiety tremor (fig 6), and a differential diagnosis may be difficult. In evaluating a tremor, it is important to examine the palms for sweating. A dry palm in an anxious patient is an anomaly.^{4b}

SUMMARY

1 A tremor, like palmar sweating, is a normal physiologic process, easily modified by outside influences.

2 Tremors vary widely according to their rate, amplitude and pattern. Under emotional influences the variation is chiefly with respect to amplitude.

3 A tremor of high amplitude was demonstrated in widely selected groups of army personnel, but the highest incidence was found among emotionally disturbed soldiers.

4 An excessive palmar sweat response and a tremor of high amplitude were found to exist together in the same patient almost exclusively in the group suffering from anxiety features (neurocirculatory asthenia). This combination was not found in any of the normal persons.

5 A tremor takes on clinical significance only when it is correlated with other signs. In evaluating a tremor, it is important to examine the palms for sweating.

15 Lazarus, S., and Bell, G. H. Tremor in Hyperthyroidism, Glasgow M. J. 140 77, 1943.

16 Wolf, W. Endocrinology in Modern Practice, Philadelphia, W. B. Saunders Company, 1936.

17 Dunn, W. H. Emotional Factors in Neuro-Circulatory Asthenia, Psychosom. Med. 4 333, 1942.

18 Wood, P. Etiology of Da Costa Syndrome, Brit. M. J. 1 845, 1941.
Grinker, R. R. and Spiegel, J. P. War Neurosis, Philadelphia, The Blakiston Company, 1945.

PERNICIOUS ANEMIA IN THE TROPICAL NEGRO

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ACCORDING to most published data, pernicious anemia appears to have an uneven distribution in different parts of the world, being a disease chiefly of the temperate zone, more particularly North America, the British Isles and Northern Europe. Information concerning its incidence in the tropics is meager in the better known textbooks of medicine. In addition to this lack of knowledge, there are divergent opinions as to the role that race plays in the distribution of the disease, especially in relation to the frequency among Negroes.

From a review of the literature, the prevailing impression is gained that the incidence of the disease in Negroes is increased in proportion to the amount of intermixture with white persons. Cornell¹ quoted Longcope as saying that pernicious anemia seldom if ever occurs in full-blooded Negroes. Kracke² adhered to this same view and stated that after a careful watch for the disease at the Grady Hospital in Atlanta, Ga., for the past ten years he has not observed a case among a large number of Negroes admitted. However, Wintrobe³ felt that the rareness of the occurrence of pernicious anemia in full-blooded Negroes has been overemphasized. He presented 33 cases involving Negroes among a total of 329 patients with the disease admitted to the Johns Hopkins Hospital between the years 1925 and 1940. At Peter Bent Brigham Hospital, Friedlander⁴ reviewed 500 cases of the disease among a total of 80,145 persons admitted, of which 4,503 were Negroes. Only 3 Negroes with pernicious anemia, or 0.07 per cent of the total number admitted, were found. Kampmeier and Cameron⁵ studied the number of patients with pernicious anemia admitted to the Louisiana State Charity Hospital during the decade 1926 to 1936. They reported 98 cases of the disease among the white persons and 14 among the Negroes.

From Gorgas and Colon hospitals, Panama Canal Health Department, Cristobal, Canal Zone

1 Cornell, B. S. *Pernicious Anemia*, Durham, N. C., Duke University Press, 1927

2 Kracke, R. R. *Diseases of the Blood and Atlas of Hematology*, ed. 2, Philadelphia, J. B. Lippincott Company, 1941

3 Wintrobe, M. M. *Clinical Hematology*, Philadelphia, Lea & Febiger, 1943

4 Friedlander, R. D. *Racial Factor in Pernicious Anemia*, *Am J M Sc* **187** 634, 1934

5 Kampmeier, R. H., and Cameron, P. B. *Pernicious Anemia in the Negro*, *Am J M Sc* **192** 751, 1936

The disease occurred seven times more frequently among the white patients since an equal number of white persons and Negroes were admitted. Schwartz and Gore⁶ reviewed the literature up to 1943 and found 106 reported cases of pernicious anemia among Negroes. They studied 1,000 consecutive patients with this disease who entered Cook County Hospital in the interval from 1931 to 1942 and found 93 of them to be Negroes. The ratio of white persons to Negroes in their series was about 10 to 1.

Pernicious anemia is extremely uncommon among natives of tropical and oriental countries.⁷ Strong⁸ quoted from a report on anemias of the tropics made by Dr. De Langen and Dr. Lichenstein in Java in which they stated that they have never observed a case of pernicious anemia in a native. They also related that pernicious anemia does not occur among the Negro races in Africa, but occasionally it has been found in certain of the tribes in the neighborhood of Lake Tanganyika. Wills⁹ has described a tropical macrocytic anemia in India which is almost indistinguishable from pernicious anemia both clinically and hematologically. Because of the multiplicity of complicating disorders she has been unable to classify this anemia more definitely.

The problem of determining what persons should be included under the term Negro is one of great magnitude. It was not possible to ascertain the presence or percentage of admixture of white and Negro blood with any degree of certainty, but we can state that the overwhelming majority of our patients were of Negro parentage and came from a native Negro habitat. In addition, we employed as our criteria a combination of the anthropologic¹⁰ definition of the Negro and the commonly accepted clinical characteristics such as the dark brown to sooty black skin, flat broad nose, everted lips, woolly hair, prognathous jaws with large teeth, dark eyes and the typical negroid facies.

SELECTION OF CASES

The diagnostic criteria employed in the selection of cases were those which have been well established for the disease. Clinical recognition

6 Schwartz, S. O., and Gore, M. Pernicious Anemia in Negroes, *Arch. Int. Med.* 72: 782 (Dec.) 1943.

7 Kracke,² Wintrobe,³ Friedlander.⁴

8 Strong, R. P. *Stitt's Diagnosis, Prevention and Treatment of Tropical Diseases*, ed. 7, Philadelphia, The Blakiston Company, 1945.

9 Wills, L., and Evans, B. D. F. Tropical Macrocytic Anemia, *Lancet* 2: 416, 1938.

10 *Encyclopaedia Britannica*, ed. 14, New York, Encyclopaedia Britannica, Inc., 1929. Kroeber, A. L. *Anthropology*, New York, Harcourt, Brace & Company, 1923. Haddon, A. C. *The Races of Man*, New York, The Macmillan Company, 1925.

was based on symptoms referable to the anemia and to the gastrointestinal and neurologic systems, with 3 of the patients having varying degrees of subacute combined sclerosis. Achlorhydria following the injection of histamine was present in all cases except case 1, in which the diagnosis was made at necropsy. Examination of the blood revealed a macrocytic anemia, with an increased mean corpuscular volume and mean corpuscular hemoglobin content. Peripheral blood smears revealed anisocytosis and poikilocytosis. Leukopenia and thrombopenia were present in 3 cases. Three patients had elevated icteric indexes, which returned to normal after therapy. In 6 cases, including 2 at necropsy, the structure of the bone marrow was characteristic of pernicious anemia. The stools were normal, and in only 1 case were parasites found. The parasite was *Trichuris trichiura*. Roentgenograms of the upper gastrointestinal tract were made in 8 cases and found to be normal. The therapeutic test using parenterally administered liver was employed and was followed by reticulocytosis, rapid relief of symptoms and a rise in the red blood cell count (table).

REPORT OF CASES

CASE 1—L. H., a 66 year old Jamaica-born Negro woman, was admitted to the hospital because of severe asthenia and dyspnea. Examination showed the patient to be malnourished and dehydrated and to appear gravely ill. The mucous membranes of the mouth were pale, and the tongue was heavily coated and dehydrated. The scleras appeared icteric. The hemoglobin content was 3.75 Gm per hundred cubic centimeters, the red blood cell count 1,200,000 and the white blood count 7,800, with 57 per cent neutrophils and 43 per cent lymphocytes. A smear did not reveal malaria, and the peripheral blood smear revealed many nucleated red cells. The patient died in her sleep the evening of her admission to the hospital before any further studies could be made. Autopsy revealed considerable megaloblastic proliferation of the bone marrow, lemon yellow-colored fat and a moderate hemosiderosis of the internal organs. The cause of death was pernicious anemia.

CASE 2—G. M., a 51 year old Barbadian-born Negro, was admitted to the hospital because of progressive dyspnea and paresthesias of the lower extremities of three months' duration. The latter became so severe that he was unable to walk unaided. The past history disclosed an untreated penile lesion. Examination revealed a senile, oriented, chronically ill man. An enlarged heart was present, with a systolic aortic blowing murmur. There was ataxia of both upper and lower extremities, with muscle weakness, a tabetic gait and positive reactions to the Romberg and the finger to nose tests. The pupils reacted well, and all deep tendon reflexes were absent. A hemogram revealed a hemoglobin content of 7.5 Gm per hundred cubic centimeters, a red blood cell count of 2,350,000 and a white blood cell count of 5,200, with 62 per cent neutrophils, 2 per cent eosinophils and 36 per cent lymphocytes. The reticulocyte count was 0.7 per cent, and the volume index was 1.255. The peripheral blood smear did not reveal malaria or the sickling trait but did reveal anisocytosis and macrocytosis. The mean corpuscular

Data in 10 Cases of Pernicious Anemia

Case	Sex	Age	Place of Birth	Year of Admission	Blood Admixture*	Hemoglobin Content, Gm/100 Cc		Red Blood Cells, Millions/Cu Mm		Reticulocytosis %		Hematocrit, Cc/100 Cc		Mean Corpuscular Volume in Cubic Microns on Admission	Mean Corpuscular Hemoglobin in Micrograms on Admission	Bone Marrow	Roentgenograms of the Upper Gastrointestinal Tract	Achlorhydria
						Admission	Discharge	Admission	Discharge	Admission	Maximum	Admission	Discharge					
1	F	66	Jamaica	1933	0	3.75	-----	1.2	-	-----	-	-----	-----	-----	-----	Diagnostic (necropsy)	-----	-
2	M	51	Barbados	1942	+	7.5	11.5	2.35	4.08	0.7	5.0	32	41	130	32.6	Not examined	Normal	+
3	M	41	St. Vincent's	1943	+	5.4	10.5	2.2	4.0	1.1	8.6	24	40	100	26	Diagnostic	Normal	+
4	M	50	Barbados	1944	+	5.25	9	1.9	3.5	-----	7.6	-----	-----	-----	-----	Diagnostic (necropsy)	Normal	+
5	M	51	Barbados	1946	+	2.9	13	0.92	4.2	2.6	28	9.5	- - -	103.2	31.5	Diagnostic	Normal	+
6	M	47	Colombia	1946	-	6.7	12.6	2.26	3.53	0.1	15.1	21	-----	93	29	Unsatisfactory examination	Normal	+
7	F	55	Jamaica	1947	-	5.6	12.6	1.35	4.47	0.1	37	15	-----	118	41	Not examined	Normal	+
8	M	55	Barbados	1947	+	6.5	14.8	1.99	4.23	0	7	17	37	90	34.2	Diagnostic	Normal	+
9	M	60	Panama	1947	+	5.6	13.2	1.26	3.82	0.5	16.6	13	-----	103	44	Not examined	Normal	+
10	M	70	Barbados	1947	+	3	9	1.02	3.0	1	35	11	-----	104	33	Diagnostic	Unsatisfactory	+

*The plus sign means that both parents were Negroes the minus sign that one parent was 50 per cent Caucasian and the zero that no knowledge relating to the parents was obtained

hemoglobin was 32.6 micromicrograms. Achlorhydria was present after the administration of histamine. The reaction of the blood to serologic tests was positive, but examination of the spinal fluid revealed it to be normal. Roentgenograms of the upper gastrointestinal tract were normal. Liver therapy was instituted, and eight days later a reticulocyte count of 5 per cent was noted. Neurologic consultation confirmed the original findings, and a diagnosis of subacute combined sclerosis was made. The hemoglobin content and the red blood cell count progressively increased to 11.5 Gm and 4,080,000 cells respectively two months after treatment was started. The mean corpuscular volume was 97.3 cubic microns and the mean corpuscular hemoglobin 31.6 micromicrograms. Reevaluation by the neurologic department demonstrated a normal gait, with a return of the vibratory sensation. The patient felt clinically well and was discharged to the outpatient department for observation.

CASE 3—I S, a 41 year old St. Vincentian-born Negro, was admitted to the hospital because of a traumatic amputation of his left foot. The physical condition was normal except for the partial loss of the affected limb. A hemogram made on his admission revealed a hemoglobin content of 10.5 Gm and 3,240,000 red blood cells. The white blood cell count was 9,450, with 78 per cent neutrophils, 2 per cent eosinophils and 20 per cent lymphocytes. His convalescence was benign except for an unexplained anemia which progressively developed five weeks after admission. The hemoglobin content dropped to 7.5 Gm and the red blood cell count to 2,000,000. The white blood cell count was 3,250, with a normal differential count. Repeated analyses of the stools showed them to be normal. Examination revealed glossitis and a low grade fever, the temperature fluctuating to 99.6 F. The patient was given ferrous sulfate and vitamin therapy, which had no effect on the progression of the anemia. Eight weeks after admission examination revealed pronounced diminution of vibratory sensation in the right ankle. The hemoglobin value had fallen to 5.4 Gm and the red blood cell count to 2,200,000. The reticulocyte count was 1.1 per cent, and the blood smear revealed anisocytosis and poikilocytosis. Gastric analysis revealed achlorhydria after the administration of histamine. The hematocrit value was 24. The mean corpuscular volume was 109 cubic microns, the mean corpuscular hemoglobin was 26 micromicrograms and the mean corpuscular hemoglobin concentration was 23 per cent. Liver therapy was instituted, and three days later the reticulocyte count was 8.1 per cent. Daily reticulocyte counts revealed a fluctuation from 8.1 per cent on the third day of therapy to 8.6 per cent on the eighth day. The reticulocytosis gradually declined so that twenty days after the institution of therapy the count was 0.6 per cent. The hemogram showed progressive improvement, and eighteen days after administration of liver was begun the hemoglobin content was 9.0 Gm per hundred cubic centimeters and the red blood cell count 3,380,000. The patient felt much improved, and the tongue was no longer smooth. Six weeks after therapy was instituted, the vibratory sensation returned to normal. The hemoglobin content was 10.5 Gm per hundred cubic centimeters and the red blood cell count 4,000,000. The reticulocyte count was 0.7 per cent and the hematocrit value 40. The mean corpuscular volume was 105.3 cubic microns, the mean corpuscular hemoglobin 31.6 micromicrograms and the mean corpuscular hemoglobin concentration 30 per cent. The patient was discharged to the outpatient department for follow-up and continued therapy. He has been subsequently admitted to the hospital twice, once for revision of the stump and the second time for an exacerbation of his anemia. The hemoglobin content was 4.0 Gm per hundred cubic centimeters, the red blood cell count 1,450,000 and the hematocrit value 12.5. Sternal marrow puncture revealed a

picture compatible with pernicious anemia. A series of gastrointestinal roentgenograms was normal. The patient responded well to transfusions and to liver therapy. At the time of his discharge to the clinic he had a hemoglobin content of 11.5 Gm per hundred cubic centimeters, a red blood cell count of 3,700,000 and a hematocrit value of 39.

CASE 4—C. T., a 50 year old Barbadian-born Negro, complained of progressive weakness, anorexia, loss of weight and dyspnea for five months. On examination, the patient appeared malnourished, dyspneic and acutely ill. There was a decided pallor of all the mucous membranes as well as a shiny tongue with atrophic papillae. A hemogram revealed a red blood cell count of 1,900,000 and a hemoglobin content of 5.25 Gm per hundred cubic centimeters. The white blood cell count was 5,350, with 67 per cent neutrophils, 1 per cent eosinophils and 32 per cent

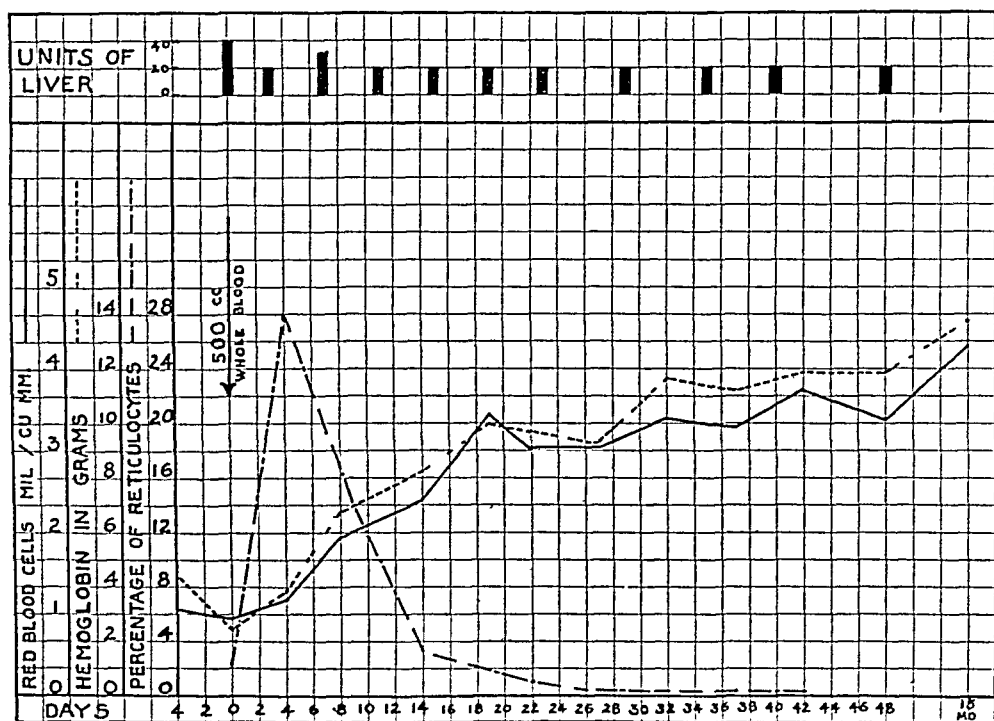


Chart 1—Hemoglobin content and red blood cell and reticulocyte counts after the institution of liver therapy

lymphocytes. The volume index was 1.06. The peripheral blood smear revealed considerable anisocytosis and poikilocytosis. Achlorhydria was present. Roentgenograms of the upper gastrointestinal tract were normal. The patient was placed on liver therapy, and a reticulocyte count of 7.6 per cent was observed three days after. Nine days after therapy was begun the reticulocyte count was 3.6 per cent and six days later it was 3.1 per cent. At the conclusion of twenty-six days of liver therapy, the value for the hemoglobin had risen to 9 Gm and the red blood cell count to 3,500,000. The patient felt clinically well and was discharged to the outpatient department for liver therapy and follow-up. He returned to the clinic occasionally and then ceased coming. He was readmitted with an exacerbation of his anemia and died shortly after.

Necropsy revealed a hemosiderosis of the viscera and a megaloblastosis of the bone marrow. The cause of death was pernicious anemia.

CASE 5—J J, a 51 year old Barbadian-born Negro, was admitted to the hospital because of progressive dyspnea and asthenia of one month's duration, complicated by disorientation and semistupor of three days' duration (chart 1) Examination revealed the patient to be poorly nourished and to appear both acutely and chronically ill The scleras were icteric, and the edges of the tongue were smooth and red Sensation could not be evaluated because of the patient's confused and disoriented mental condition Laboratory study revealed a hemoglobin content of 2.9 Gm per hundred cubic centimeters, a red blood cell count of 920,000 and a hematocrit value of 9.5 The white blood cell count was 5,050, with 54 per cent neutrophils, 45 per cent lymphocytes and 1 per cent eosinophils The mean corpuscular volume was 103.2 cubic microns, the mean corpuscular hemoglobin 31.5 micromicrograms and the mean corpuscular hemoglobin concentration 30.5 per cent The peripheral smear revealed anisocytosis and poikilocytosis and no malarial parasites The reticulocyte count was 2.6 per cent and the icterus index was 15 units The platelet count was 60,000 per cubic millimeter The bleeding, coagulation and prothrombin times were normal Repeated examination of the stools showed them to be normal The blood calcium was 11 mg and the non-protein nitrogen 51.7 mg per hundred cubic centimeters Achlorhydria was found after histamine was given Sternal marrow puncture revealed megaloblastosis, and the picture was interpreted as compatible with a diagnosis of pernicious anemia The electrocardiogram demonstrated a complete auriculoventricular dissociation Liver therapy was instituted, and two days after admission 500 cc of whole blood was given The value for the hemoglobin rose to 5 Gm and the red blood cell count to 1,240,000 Four days after liver therapy was started a reticulocyte count of 28 per cent was obtained The nonprotein nitrogen had fallen to 22 mg per hundred cubic centimeters The patient was remarkably improved, and his mental condition appeared normal The hemoglobin content and the red blood cell count showed a progressive rise while the reticulocyte count approached a normal level Two weeks after treatment was instituted, the value for the hemoglobin had risen to 7.5 Gm and the red blood cell count to 2,400,000 whereas the reticulocyte count was 3.1 per cent The icterus index was now normal A series of roentgenograms of the upper gastrointestinal tract was made and found to be normal A repeat electrocardiogram revealed a return to sinus rhythm One month after his admission the patient felt well and was discharged His hemoglobin content was 11.7 Gm per hundred cubic centimeters, the red blood cell count 3,690,000 and the reticulocyte count 0.3 per cent at this time The patient has been followed for fifteen months, and up to the time of this report he has felt perfectly well, with a hemoglobin content of 13.8 Gm per hundred cubic centimeters and a red blood cell count of 4,200,000

CASE 6—P P a 47 year old Colombian Negro, was admitted to the hospital with the complaint of weakness, vertigo, sore tongue and paresthesias in the finger tips for one week Physical examination revealed the patient to be chronically ill The scleras were icteric, and the mucous membranes of the conjunctivas and mouth were pale The tongue was smooth and red The hemogram showed 6.7 Gm of hemoglobin per hundred cubic centimeters, with 2,260,000 red blood cells The white blood cell count was 5,050, and there were 64 per cent neutrophils, 2 per cent eosinophils and 34 per cent lymphocytes in the differential count The peripheral blood smear revealed pronounced poikilocytosis, anisocytosis and polychromasia The mean corpuscular volume was 93 cubic microns, the mean corpuscular hemoglobin 29 micromicrograms and the mean corpuscular hemoglobin concentration

31 per cent The reticulocyte count was 0.1 per cent, and the prothrombin time was normal The icterus index was 12 and the hematocrit value 21 Examination of the stool disclosed *Trichuris trichiura* but no occult blood On gastric analysis, no free acid was found after histamine was given Roentgenograms of the gastrointestinal tract were normal The parenteral administration of liver was started Seven days after this treatment was begun the reticulocyte count reached a peak of 15.1 per cent and thereafter steadily decreased On the twentieth day of treatment the value for hemoglobin was 12.6 Gm, the red blood cell count 3,530,000 and the icterus index 2 Clinical improvement was striking, with remission of all symptoms The patient was discharged, and a follow-up examination five months later revealed a hemoglobin content of 13.4 Gm per hundred cubic centimeters and a red blood cell count of 4,200,000

CASE 7—I M, a 55 year old Jamaican-born woman, was admitted to the hospital complaining of progressive dyspnea, orthopnea and dependent edema for one week The past history revealed intermittent tenderness and stiffness in both legs for several months Physical examination revealed a poorly nourished, severely ill woman with acute dyspnea The skin and mucous membranes were pale, and the veins of the neck were distended There was dulness at the base of both lungs, and many moist inspiratory rales were heard throughout the pulmonary fields The blood pressure was 180 systolic and 100 diastolic and the pulse rate 135 The heart was markedly enlarged, and there was a precordial grade III blowing systolic murmur Ascites was present, and there was edema of all extremities and of the abdominal wall The hemogram on admission showed 4.4 Gm of hemoglobin per hundred cubic centimeters, with 1,530,000 red blood cells The white blood cell count was 10,600, with 53 per cent neutrophils, 2 per cent eosinophils, 44 per cent lymphocytes and 1 per cent monocytes The presence of anisocytosis and poikilocytosis was revealed in the peripheral blood smear The patient was treated with oxygen, digitalis, mercurial diuretics and morphine On the third day in the hospital, while still in congestive heart failure, she received a transfusion of 250 cc of whole blood, without any appreciable change in the hemoglobin content Three additional transfusions were given, which resulted in a slight increase in the hemoglobin to 7.0 Gm and in the red blood cell count to 1,720,000 She regained cardiac compensation, but the severe anemia persisted Examination of the stools occasionally revealed occult blood, but roentgenologic examination of the gastrointestinal tract disclosed no intrinsic lesion Gastric analysis showed no free acid after histamine was given A loss of the vibratory and the position sense in the lower extremities was found Four weeks after admission the value for hemoglobin was 5.6 Gm and the red blood cell count 1,350,000 The white blood cell count was 7,100, with a normal differential count, but the anisocytosis and poikilocytosis were still present The reticulocyte count was 0.1 per cent, and the hematocrit value was 15 The mean corpuscular volume was 118 cubic microns, the mean corpuscular hemoglobin 41 micromicrograms and the mean corpuscular hemoglobin concentration 37 per cent The platelet count, bleeding and coagulation times and prothrombin time were normal Liver therapy was begun, and four days later the reticulocyte count had reached 8.1 per cent This rise increased progressively, so that nine days after treatment was started the reticulocyte count had reached 39 per cent The reticulocytosis then declined, and twenty days after the beginning of treatment the count had fallen to 0.5 per cent Eight weeks after therapy was begun the patient felt clinically well Vibratory and position sense had improved considerably The value for hemoglobin at this time was 12.6 Gm and the red blood cell count 4,470,000 She was discharged to be followed as an outpatient

CASE 8—J R, 55 year old Barbadian-born Negro, sought admission to the hospital because of progressive asthenia, paresthesias of his lower extremities and vertigo associated with transitory episodes of syncope, all of one week's duration (chart 2) The past history revealed that he had been previously admitted to the hospital for a severe undiagnosed anemia, which responded to liver therapy He failed to continue specific therapy after his discharge, and this exacerbation had occurred Examination on admission showed a poorly nourished man with an ataxic gait who appeared chronically ill The edges of the tongue were smooth and red There was a loss of position and vibratory sensation The finger to nose test revealed abnormality, and the Romberg test elicited a positive reaction The hemoglobin content was 65 Gm per hundred cubic centimeters and the red

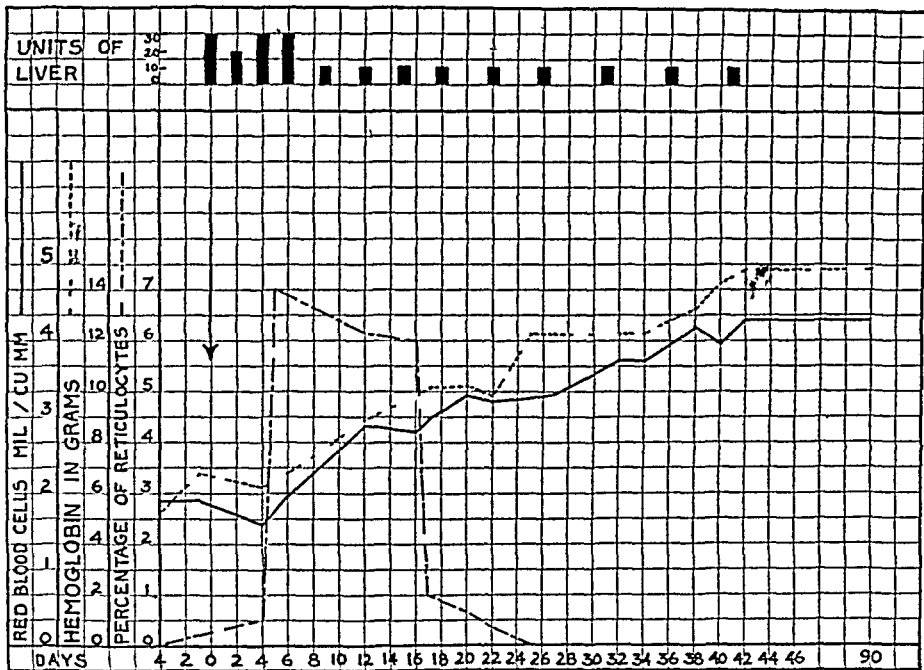


Chart 2—Hemoglobin content and red blood cell and reticulocyte counts after the institution of liver therapy

blood cell count 1,990,000 The white blood cell count was 3,600, with 43 per cent neutrophils, 2 per cent basophils, 2 per cent eosinophils and 53 per cent lymphocytes The hematocrit value was 17, and the platelet count was 87,000 per cubic millimeter The mean corpuscular volume was 90 cubic microns, the mean corpuscular hemoglobin 34.2 micromicrograms and the mean corpuscular hemoglobin concentration 38.2 per cent A blood smear revealed anisocytosis, poikilocytosis and polychromasia, no reticulocytes were evident The bleeding, coagulation and prothrombin times were normal The icterus index was normal, as were the stools on repeated examination No free hydrochloric acid was demonstrable after administration of histamine A series of roentgenograms of the upper gastrointestinal tract was normal Sternal marrow puncture revealed megaloblastosis and several multilobed neutrophilic leukocytes, and the picture was interpreted as compatible with pernicious anemia Liver therapy was begun,

and four days later the reticulocytes numbered 7 per cent. The hemoglobin content and the red blood cell count increased, so that ten days after therapy was initiated they were 8.5 Gm and 2,980,000 respectively. The reticulocyte count was 4.2 per cent. The patient felt much stronger and was now able to walk unaided. His course became one of steady, progressive clinical and hematologic improvement so that he was able to be discharged six weeks after specific therapy was instituted. His gait was normal, as was the reaction to the Romberg test. The vibratory sensation was still somewhat diminished but was much improved since his admission. The hemoglobin content was 14.8 Gm per hundred cubic centimeters and the red blood cell count 4,230,000, and no reticulocytes were seen. He has been followed for three months as an outpatient, and his blood picture has remained the same. He has regained almost complete return of his vibratory sensation.

CASE 9—R. S., a 60 year old Panamanian Negro, was admitted to the hospital with the complaints of progressive weakness and dyspnea of one month's duration. Nine years prior to this admission, a diagnosis of pernicious anemia had been made in another hospital and treatment with liver instituted. He had taken treatment intermittently, but for several months before this admission he had received no liver therapy. Physical examination showed a well nourished and well developed man who appeared chronically ill. The conjunctivas and mucous membranes of the mouth were pale, and the edges of the tongue were smooth. The vibratory sensation was absent in the lower extremities. The hemoglobin content was 5.6 Gm per hundred cubic centimeters, the red blood cell count 1,260,000 and the white blood cell count 9,200, with 83 per cent neutrophils, 16 per cent lymphocytes and 1 per cent monocytes. A blood smear showed anisocytosis, poikilocytosis and polychromasia. The hematocrit value was 13, the mean corpuscular volume 103 cubic microns, the mean corpuscular hemoglobin 44 micromicrograms and the mean corpuscular hemoglobin concentration 43 per cent. The reticulocyte count was 0.5 per cent, and the icterus index was 15 units. On gastric analysis there was no free acid present after the administration of histamine. On the day after his admission treatment with liver extract was begun. However, by the fourth hospital day the value for hemoglobin had decreased to 4.0 Gm and the red blood cell count to 818,000. After a transfusion of 500 cc of whole blood the hemoglobin increased to 8.6 Gm and the red blood cell count to 2,240,000. Seven days after treatment was started the reticulocyte count reached 16.6 per cent but the hemoglobin content and the red blood cell count decreased. Occasionally, occult blood was found in the stools, but roentgenograms of the gastrointestinal tract were normal. After twelve days of treatment with liver a hemoglobin value of 8.6 Gm and a red blood cell count of 2,270,000 reflected a beginning response. The reticulocyte count dropped to 1 per cent, and the icterus index returned to normal. Improvement was slow, but after forty-six days of treatment the hemoglobin value was 13.2 Gm and the red blood cell count 3,820,000. The patient felt well clinically and was discharged to be followed as an outpatient.

CASE 10—N. P., a 70 year old Barbadian-born Negro, was admitted to the hospital because of progressive weakness. Examination revealed a chronically ill, disoriented, elderly man with a blood pressure of 108 systolic and 54 diastolic. Notable glossitis was present, and a systolic blowing precordial murmur was heard. Laboratory study revealed a hemoglobin content of 3 Gm per hundred cubic centimeters, a red blood cell count of 1,020,000 and a white blood cell count of 3,700, with 60 per cent neutrophils, 4 per cent eosinophils and 36 per cent lymphocytes. The hematocrit value was 11, and the mean corpuscular volume was 104

cubic microns The mean corpuscular hemoglobin was 33 micromicrograms and the volume index 1.09 The platelet count was 138,000 per cubic millimeter, and the reticulocyte count was 1 per cent The icterus index was 8 units No free hydrochloric acid was found after histamine was given The stools were normal Poor cooperation made gastrointestinal roentgenograms unsatisfactory Sternal marrow puncture revealed an increase in megaloblasts and in multilobed neutrophils, which was interpreted as being compatible with pernicious anemia Three days after liver therapy was instituted the reticulocyte count rose to 5 per cent and four days later to 20 per cent The peak of the reticulocytosis was noted ten days after treatment was begun, when the count reached 35 per cent The patient showed a corresponding clinical improvement, with his mental condition becoming normal Liver therapy was continued, and there was a good hematologic response One month after therapy was started the hemoglobin content had reached 9 Gm per hundred cubic centimeters and the red blood cell count 3,000,000 The reticulocyte count was now 15 per cent The patient was still in the hospital under treatment at the time of this report

COMMENT

In the "Biology of the Negro" ¹¹ states "Disease tends to prove the kinship of the different races of man but at the same time clearly demonstrates some of their differences There is no illness which affects one race that may not also affect every other race although the manifestations of an illness may vary widely among races both qualitatively and quantitatively" This statement reflects our views on the incidence and occurrence of pernicious anemia in the tropical Negro The true incidence of the disease in the tropics doesn't seem to have been well presented in the sparse literature available Some of the cases described by Willis⁹ as cases of "tropical macrocytic anemia" seem to fulfil the criteria for the diagnosis of pernicious anemia Further study will probably reveal that "tropical macrocytic anemia" can be organized into several classifications, pernicious anemia being one of them

It was virtually impossible to obtain complete and accurate genealogic data on our patients, and hence there was no certainty as to the admixture of Negro and Caucasian blood Nine of our 10 patients came from the islands of the West Indies group, a native Negro habitat, and they all had Negro parents The tenth was a dark-skinned Colombian of mixed dark Colombian and West Indian parentage Clinically and anthropologically they were considered Negroes

Six of the 10 patients have been observed personally by us and 4 of them followed as outpatients for a period ranging from three to fifteen months We feel that the diagnostic criteria employed in our cases were sufficiently rigid to warrant their acceptance as instances of true perni-

¹¹ Lewis, J. H. *The Biology of the Negro*, Chicago, University of Chicago Press, 1942

cious anemia The 2 cases in which the diagnosis was made after death give credence to the idea that the disease exists among tropical Negroes

Willson and Evans¹² concluded that pernicious anemia was milder in Negroes, but Schwartz and Gore⁶ couldn't corroborate this In our study no remarkable differences were demonstrable between the expression of the disease in the tropical Negro and that in other persons except for the absence of the classic lemon-colored skin The hemoglobin value and the red blood cell count rarely attained levels of 15 Gm and 5,000,000 respectively, such as are occasionally seen in the Caucasian patient with this disease

SUMMARY AND CONCLUSIONS

- 1 Ten cases of pernicious anemia in the tropical Negro are presented
- 2 No essential differences were brought out in the manifestations of the disease in Negroes and in other races
- 3 Pernicious anemia does occur in tropical natives, and further study and increased awareness will cause it to be more frequently recognized

¹² Willson, C R, and Evans, F A Pernicious Anemia in Johns Hopkins Hospital from 1918-1922, *Bull Johns Hopkins Hosp* **35** 38, 1924

CLINICAL OBSERVATIONS IN CASES OF MASSIVE MYOCARDIAL INFARCTION

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MYOCARDIAL infarction is a dramatic episode in the course of coronary artery disease, but it is often thought of in terms of a disease entity with its own course, prognosis and treatment. With the occurrence of myocardial infarction, a new factor is introduced into the course of coronary artery disease with myocardial ischemia, namely, gross and irreparable destruction of a portion of the cardiac muscle. This damage to the myocardium determines the immediate prognosis and the ultimate outcome entirely independently of the degree and progression of coronary arteriosclerosis. Thus, the size of the area of the destroyed muscle is one of the important factors in the prognosis, yet little investigative work has been done in estimation of the size of a myocardial infarct during life.

In terms of ordinary clinical thinking, a severe attack of pain with fully developed clinical signs of myocardial infarction is usually considered as evidence of a large infarct, while milder initial attacks with less pronounced clinical and electrocardiographic signs are thought to indicate small infarcts of the myocardium. This view, however, represents speculation rather than knowledge based on clinical-pathologic correlation.

The main difficulty in approaching the problem of correlating clinical features with the anatomic findings in myocardial infarction lies in the determination of the size of the infarct at autopsy. Massive necrosis involving large sections of the myocardium can be distinguished without much difficulty, but only a detailed study of the myocardium requiring special procedures enables the pathologist to estimate the degree of myocardial involvement in smaller infarcts. It was felt, then, that useful information could be obtained by a clinical study of cases of massive infarcts of the heart, representing the most severe anatomic damage to the cardiac muscle. While this approach is only a step in the direction

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of closer clinical-pathologic correlation of myocardial infarction, it obviates the use of elaborate setups required for the study of small infarcts

This report is based on 28 unselected cases of myocardial infarction in which the pathologic diagnosis of "recent massive myocardial infarct" was made at autopsy. It covers all cases in which this diagnosis was made in the eight year period of 1937 to 1944 in the files of the department of pathology except 8 cases of massive myocardial infarction in which clinical records were inadequate for the study. These represent 21 per cent of the total of 135 cases of recent myocardial infarction found during this period.

Pathologic data consisted of a complete and detailed description of the heart, coronary arteries and other organs affected directly and indirectly by the disease, each of which was examined grossly and microscopically. Clinical records were carefully studied with special reference to the patients' past history, the initial attack of the recent myocardial infarction, the symptomatology and the course of the attack, the laboratory and electrocardiographic findings and the mode of death.

COMMENT

The important features of acute myocardial infarction can be divided into four groups: (a) the initial attack (pain, dyspnea and associated symptoms), (b) the effect of the infarct on the circulation (heart failure, shock and drop in blood pressure), (c) the constitutional reaction to tissue destruction (fever, leukocytosis and increased sedimentation rate), and (d) the electrocardiographic changes of myocardial infarction. If a close correlation existed between the extent of myocardial infarction and its clinical features, then one would expect to find a uniformity in the severity of the clinical features in cases of massive myocardial infarction.

In this series, pain (the fundamental symptom of myocardial ischemia) was present in only 22 of the 28 cases and was severe in less than half of the cases. Dyspnea was often present and was more prominent in cases in which the pain was mild or absent. In only 1 case were both pain and dyspnea recorded as severe. Nausea with vomiting and collapse was rather infrequent.

Circulatory derangement was not severe in all cases. Left ventricular failure was present in most cases, but a severe degree of it was found in 8. Right ventricular failure and shock were infrequent. Half of the patients lived one week or more after the initial attack, and many of these died not as a result of severe circulatory insufficiency but as a result of secondary complications. These occurred frequently in patients making apparently satisfactory progress.

*Summary of Clinical and Pathologic Signs in 28 Cases of Massive Myocardial Infarction**

No	Age, Sex	Summary of History	Blood Pressure	Temperature	Left Ventricular Failure	Right Ventricular Failure	Shock	White Blood Cell Count	Sedimentation Rate	Electrocardiogram	Duration Days	Pathologic Findings	Immediate Cause of Death
1	63 M	Moderately severe attack of substernal pain, nausea, vomiting, then severe dyspnea of 24 hours' duration	80/60		+++			33 200			2	Thrombus in the left coronary artery recent massive myocardial infarct of large part of left ventricle	-
2	60 M	Moderately severe pain, constriction in anterior part of the chest, severe dyspnea of 12 hours' duration	110/75	38C (100.4F)	+++			13 200 (2) 11 500 (3)	25mm W(5)	Low voltage elevated ST ₁ , deep Q ₁ , depressed ST-S-T ₃ (3)	3	Thrombus in left anterior coronary branch, recent infarct of almost entire apex of left ventricle	-
3	49 M	Pain in right side of chest with cough, night sweats, mild dyspnea of 48 hours' duration	105/70, then 95/60, toxic pressure below 100	37 to 39C (98.6 to 102.2F)	+			13 700	22mm W	Normal (2) T ₁ and T ₄ deeply inverted, T ₂ flat (21)	26	Thrombus in left anterior coronary branch, recent infarct of apex of left ventricle and entire septum multiple emboli	Femoral embolism
4	50 M	Attack of faintness, dizziness and cold perspiration of few hours' duration for a year, suffered from mild epigastric pressure on exertion	80/60	38C (100.4F)			+++	28 200	7mm W	Atypical bundle branch block, no ST deviation (3)	6	Thrombus in left anterior coronary branch, recent infarct of anterior wall of left ventricle and 2/3 of septum multiple pulmonary infarcts	Multiple pulmonary emboli
5	66 M	Moderately severe substernal pain of 16 hours' duration followed by cough, dyspnea	130/90	38C (100.4F)	+++	++	-		18mm W	Classic Q-T1 type myocardial infarct pattern, later right axis deviation, low voltage	13	Recent thrombus in left anterior coronary branch, old infarct, 6x1 cm of the posterior wall, recent infarct of anterolateral wall, left ventricle and 1/3 of septum	-
6	65 M	In hospital for carcinoma of prostate, mild exertional chest pain developed then a severe attack of pain across lower part of chest with dyspnea and weakness	80/40	-	++	--	+		-	- - -	1	Thrombus in left circumflex coronary branch, recent infarct of posterior and lateral wall of left ventricle	--
7	56 M	In hospital because of rectal bleeding, severe attack of pain in the anterior part of the chest with dyspnea, anxiety and cold perspiration	170/120	Normal		-	--	15 900	32mm W(6)	Small Q-T1, S-T ₂ , slightly elevated, S-T ₄ elevated, T ₁ , T ₄ inverted (3)	15	Thrombus in left anterior coronary branch, recent infarct of distal half of the left ventricle with a more recent hemorrhage in apical area	Sudden death

No	Age, Sex	Summary of History	Blood Pressure	Temp erature	Left Ven-tricular Failure	Right Ven-tricular Failure	Shock	White Blood Cell Count	Sedi-ment-a-tion Rate	Electrocardiogram	Dura-tion, Days	Pathologic Findings	Immediate Cause of Death
8	57 M	Mild substernal pain of 36 hours' duration attack of severe dyspnea, cough frothy sputum on admission to hospital, exertional angina for two years	100/70	38C (100.4F)	++	-	+++		-	Q waves in leads I, II, III elevated S-T segments and inverted T-waves in leads I, II IV (2), then wide and vibratory QRS complexes developed	4	Thrombus in left anterior coronary branch, recent massive myocardial infarct of anterolateral part of left ventricle, anterior part of right ventricle and lower part of the septum	--
9	73 F	Attack of severe precordial pain of three hours' duration	130/90	37.2C (98.9F)	+++ (late)	-		9 000 (2) 18 000 (7)	49mm (C)	S T segments depressed in all leads (2) Later S wave appeared in leads II and III, T1 became inverted (4)	8	Thrombus in left anterior and left circumflex coronary branches, recent infarct of most of anterolateral wall of left ventricle, basal portion of septum, old infarct, 7x2cm, in the posterior wall of left ventricle	
10	68 F	Severe epigastric and lower substernal pain with repeated vomiting and palpitation of 24 hours duration	105/70	38.5C (101.3F)	+		-	12 300	21 mm (W)	Broad S wave type, right bundle branch block with absent R4 elevated S T4 (2)	3	Thrombus in left coronary artery, recent infarct of lower 2/3 of septum, anterior portion of left ventricle and entire apex	Sudden death
11	67 F	Three days prior to admission, severe substernal pain, nausea, vomiting, similar attack 6 years previously, in bed 3 months	110/80	38.8C (101.8F) later 39 to 40C (102.2 to 104 F)	+++		--	13 000 (3) 20 000 (5)	46 mm (C)	Left axis deviation, depressed S-T1,2, inverted T1 (2), less marked S T deviation (6) normal axis, normal lead IV (9)	10	Thrombus in left circumflex coronary branch, old thrombus of left anterior branch, recent infarct, 9x9 cm, most of posterior wall of left ventricle, old infarct, 5x12 cm, in anterior wall of left ventricle	
12	54 M	Severe pain in anterior part of chest of 48 hours' duration similar attack 7 years previously untreated last 6 months exertional anginal attacks	98/78	38 to 39 C (100.4 to 102.2 F)	+		++	9 000	--	Left axis deviation, deep Q2, Q3, slight elevation of S-T2, S T3 inverted T2 3 (3)	4	Thrombus in left coronary artery, recent infarct, 12x15 cm, of distal half of septum and anterior wall of left ventricle part of posterior wall of left ventricle, scar in left ventricle wall	
13	67 M	Severe pain in anterior part of chest and left arm, dyspnea, nausea and vomiting of 24 hours' duration	90/70	38.5 C (101.3 F)	+++	--	+	15 000	32 mm (W)	Wide QRS complexes with prominent S waves slight elevation of S T4 (4)	4	Thrombus in left anterior coronary branch, recent infarct, 10x12 cm, of anterior wall of left ventricle and entire septum	
14	77 F	Severe pain in anterior part of chest and left shoulder, followed by severe dyspnea of several hours' duration	140/90	38 C (100.4 F)	+++	++		16 000		-----	3	Severe coronary sclerosis, no thrombus found, recent infarct of lower half of septum and most of anterior wall of left ventricle	

Summary of Clinical and Pathologic Signs in 28 Cases of Massive Myocardial Infarction—Continued*

No	Age Sex	Summary of History	Blood Pressure	Temperature	Left Ven-tricular Failure	Right Ven-tricular Failure	Shock	White Blood Cell Count	Sedi-mentation Rate	Electrocardiogram	Duration Days	Pathologic Findings	Immediate Cause of Death
15	68 M	Nightly attacks of severe dyspnea for one week	140/80	38 C (100.4 F)	+			7 900		Normal QRS complexes in inverted T waves in leads I, II and III normal lead IV (3)	7	Thrombus in right coronary artery recent massive myocardial infarct of most of posterior wall of left ventricle	Sudden death
16	56 M	Attack of severe pain in upper abdominal area with nausea and vomiting of several hours duration	110/80	39 C (102.2 F)	-	-	++	26 000		Classic sequence of patterns of posterior myocardial infarction	20	Thrombus in right coronary artery, recent infarct of entire posterolateral wall of left ventricle	Gastrointestinal hemorrhage
17	41 M	Series of attacks of pain in the anterior part of chest radiating to both elbows, of one week's duration, most severe for 6 hours, with vomiting at age 29, similar attack	160/100	37.5 C (99.5 F)	+	--	-	11 900	14 mm (V) (2) 29 mm (V) (12)	Left axis deviation with prominent Q2 and QS normal S-T (3) no change (5, 7)	21	Thrombus in left circumflex coronary branch, old thrombus of left anterior coronary branch recent infarct of anterior and posterior wall of left ventricle, scar in apex and lower 2/3 of septum	Cerebral embolus
18	82 F	Sudden attack of severe dyspnea nausea vomiting and cough with frothy sputum—3 hours duration	210/110	37.5 C (99.5 F)	++	--	-	16 800	--	Normal QRS complexes in inverted T waves in leads I, II, III and IV, auricular fibrillation (2)	3	Incomplete occlusion of left anterior coronary branch recent infarct of large part of posterior wall portions of anterior wall and septum	Cardiac rupture
19	79 M	While in hospital recovering from prostatectomy had sudden attack of severe dyspnea cyanosis apprehension and cough	200/100	--	+++	--	--	--	--	Normal QRS complex, depressed RS-T segment in leads I, II and IV, normal T waves (2)	8	Thrombus in right coronary artery old thrombus in left anterior coronary branch, recent infarct of posterolateral wall of left ventricle scar (small) at apex	Multiple emboli systemic and pulmonary
20	73 M	Attack of severe dyspnea of 24 hours' duration within past two weeks several mild attacks of nocturnal dyspnea	140/100 100/65	39 C (102.2 F)	++	++	--	20 000 (2) 15 000 (5)	--	Marked left axis deviation, small R4, T1 inverted (2)	8	Thrombus in left circumflex coronary branch recent infarct of most of left ventricle	Multiple emboli systemic and pulmonary
21	66 M	Attack of severe pain in anterior part of the chest left scapula, neck, both arms—3 hours' duration patient known to have hypertension	140/100	37.5 C (99.5 F)	+	--	--	17 800	-	Left axis deviation, absent R4 markedly elevated RS-T segment in leads I and IV (2)	3	Thrombus in left anterior coronary branch recent infarct of anterior 2/3 of left ventricle wall, entire apex and lower septum	Cardiac rupture

No	Age, Sex	Summary of History	Blood Pressure	Temperature	Left Ven-tricular Failure	Right Ven-tricular Failure	Shock	White Blood Cell Count	Sedimentation Rate	Electrocardiogram	Duration, Days	Pathologic Findings	Immediate Cause of Death
22	54 M	Collapsed three weeks prior to admission, severe dyspnea and orthopnea, which persisted	110/70 (20)	37.5 C (99.5 F)	+++	--	--	5 600 (20)	--	-----	22	Thrombus in left anterior coronary branch, recent massive myocardial infarct of most of anterior wall of left ventricle, 2/3 of septum	
23	60 M	Severe epigastric pain with extremedyspnea of 3 hours' duration, milder attacks of pain for few weeks	115/80	(38 C) (100.4 F)	+++	--	--	12,400	--	Left axis deviation, flat T1 (2)	2	Thrombi in left anterior coronary branch and left circumflex coronary branch, recent infarct of most of posterolateral wall of left ventricle	Sudden death
24	76 M	Excruciating pain in upper abdominal and lower chest areas radiating to both arms, nausea and vomiting of 12 hours' duration	80/60	38 C (100.4 F)	+	-	+	18 000 (W)	20 mm (W)	Left bundle branch block, with small Q1,4 slight elevation of S-T2,3 (2)	3	Thrombus in left circumflex coronary branch, old thrombus in left anterior coronary branch, recent infarct of posterior half of left ventricle	
25	66 M	Attack of moderately severe burning pain in anterior part of chest, with weakness—24 hours' duration, patient known to have hypertension	110/70	38 C (100.4 F)	+	--	--	11 400 (4) 15,200	21 mm (W)	Q waves present in leads I, II, III, elevation of S-T segment in leads I, II, and IV, T3 inverted (3), T waves inverted in all 4 leads (7)	13	Thrombus in left anterior coronary branch, recent infarct of entire anterior wall of left ventricle	Perforation of heart
26	63 M	Series of attacks of severe pain in anterior part of chest over period of 4 days	130/90	39 C (102.2 F)	++	-	--	19 800	10 mm (W)	Atypical bundle branch block, no S-T deviations, no change in pattern (2,6)	12	Thrombus in left anterior coronary branch, recent infarct of anterior 2/3 of septum, most of anterior wall of left ventricle and some of right ventricle	Empyema
27	56 M	Attack of severe chest pain, dyspnea, nausea and vomiting of 3 hours' duration, similar attack 9 years previously	130/90	39 C (102.2 F)	++	+	--	15,300	31 mm (W) (5)	Left axis deviation, prominent Q2 Q53, inverted T2, T3 (2)	20	Thrombus in right coronary artery, old thrombus in left anterior coronary branch, recent infarct of all posterolateral wall of left ventricle, scar at apex	Cerebral embolism
28	52 M	Attack of severe pain in anterior part of chest of 4 hours' duration, lesser attacks for several weeks, 6 months previously had myocardial infarction	160/110	38.5 C (101.3 F)	+	--	--	24 000 (2)	17 mm (W)	Left axis deviation deep Q2, Q3 elevated S-T segment in leads I, II and III, inverted T1,4 (2)	3	Thrombus in left circumflex coronary branch old thrombus in left anterior coronary branch recent infarct of entire distal half of left ventricle, scar in apical portion of left ventricle	

Fever was present in 27 of the 28 cases, but the elevation of temperature was on the average mild. In only 10 cases did the temperature reach or exceed 39 C (102.2 F). A high degree of leukocytosis (20,000 cells or over) was found in less than half of the cases in which blood counts were recorded. Also, the sedimentation rate was not persistently elevated.

Electrocardiographic findings in the 24 cases in which records were available had to be interpreted with great care, because only four lead electrocardiograms were available. Present day emphasis on exploration of the thoracic wall with semidirect leads makes four lead electrocardiography seem incomplete, yet the three standard limb leads are still the basis and the essential part of the electrocardiogram and are of particular value in myocardial infarcts of the posterior wall. In this series 4 patients showed the classic pattern of myocardial infarction, 5 had atypical changes, with RS-T deviation and T wave changes supporting the clinical diagnosis of myocardial infarction, 3 had depression without elevation of the RS-T segments, making the record equivocal, 7 had no RS-T changes whatsoever and only equivocal T wave changes and, finally, 5 had bundle branch block patterns with or without displacement of the RS-T segments. It is striking that in this small series of cases of massive myocardial infarcts the classic patterns of acute myocardial infarction in the standard limb leads were uncommon, atypical and even nondiagnostic patterns were present in the majority of cases, with almost all tracings taken at the time when maximum changes were to be expected. Doubtless, serial precordial leads taken in some of these cases would have shown changes indicative of myocardial infarction which were not present in the standard four lead electrocardiogram, but this would not have altered the general trend of the electrocardiographic findings.

In order to estimate the over-all severity of the clinical picture of myocardial infarction, an arbitrary scoring was devised. With the omission of electrocardiographic signs, which could not be scored satisfactorily, the three groups of features of myocardial infarction (initial attack, circulatory derangement, constitutional reactions) were scored thus: 1, mild or absent, 2, moderately severe, and 3, severe. Thus the mildest manifestations of myocardial infarction were scored as 3 and the most severe as 9. As a result of this scoring 6 patients were classified as having mild disease (scores 3 and 4), 14 patients as having

Footnote for Table

*W indicates Wintrobe method and C Cutler method. Number in parentheses following various laboratory readings and electrocardiographic descriptions indicates the number of days after the presumed onset of the recent myocardial infarction. "Duration" indicates the time elapsing between the presumed onset of myocardial infarction and death. "Sudden death" is recorded only for patients not appearing seriously ill and is presumed to be caused by ventricular fibrillation.

moderately severe disease (scores 5 and 6) and 8 as having severe disease (scores 7, 8 and 9). Three patients had a score of 3, and 2 patients were given a score of 9.

This analysis is perhaps the best way of showing that massive myocardial infarction does not necessarily run the course of a severe, uniformly fatal illness. It also suggests that the relationship between the severity of clinical manifestations and the extent of myocardial infarction is far less simple than is generally assumed. It is evident that none of the various clinical features of myocardial infarction has occurred in a characteristic form, nor has an unusual severity of them been frequent enough to be of aid in the diagnosis of massive myocardial infarction.

The severity of the initial attack, the effect of the infarction on the circulation and the constitutional reactions to it are obviously affected by additional factors other than the size of the necrotic area of the myocardium. It is not clear what the nature of these factors is. It was shown in another report¹ that patients with preexisting cardiac disease such as hypertension with cardiac hypertrophy or old myocardial scars from previous infarcts, do not respond differently to a new infarction than those who had no evidence of myocardial disease prior to the fatal infarction. This is fully confirmed in this series. It has also been suggested that the degree of coronary arteriosclerosis bears no obvious relationship to the immediate prognosis of acute myocardial infarction. Individual variations in the response to myocardial ischemia and injury and in the ability to compensate for its effect on the circulation may play an important role in explaining the discrepancy between the degree of myocardial damage and the clinical manifestation and course. An interesting possibility is suggested by the work of Rosenbaum, Johnston and Wilson,² who presented electrocardiographic evidence that myocardial infarction may develop over a period of a few days. A gradually developing myocardial infarction or a smaller infarct with a secondary extension may perhaps have a less profound effect on the circulation and give rise to fewer symptoms and constitutional reactions than myocardial necrosis of equal extent developing all at once. In the correlation of clinical features with pathologic findings of myocardial infarction, it should be noted that Robb and Robb³ and Lowe and Wartman⁴ expressed

1 Selzer, A. The Immediate Sequelae of Myocardial Infarction. Their Relation to the Prognosis, *Am J M Sc* **216** 172 (Aug) 1948.

2 Rosenbaum, F. F., Wilson, F. N., and Johnston, F. D. Changes in the Precordial Electrocardiogram Produced by the Extension of Anteroseptal Myocardial Infarction, *Am Heart J* **30** 11 (July) 1945.

3 Robb, J. S., and Robb, R. C. Localization of Cardiac Infarcts in Man. I. Comparison of Anterior-Posterior with Muscle Bundle Modes of Localization, *Am J M Sc* **197** 7 (Jan) 1939, II. Twenty-Nine New Cases of Muscle Bundle Localization with Postmortem Confirmation, *ibid* **197** 18 (Jan) 1939.

4 Lowe, T. E., and Wartman, W. B. Myocardial Infarction, *Brit Heart J* **6** 115 (July) 1944.

the opinion that some specific myocardial muscle bundles may have important functions. However, this factor need not be considered in the interpretation of massive myocardial infarction in which all layers of the myocardium were destroyed over large areas.

It is shown that typical electrocardiographic patterns are not a common feature of massive myocardial infarcts and presumably occur more often in smaller infarcts. This is best explained by assuming that a simultaneous involvement of various regions of the heart causes cancellation of certain electrocardiographic changes, involvement of sections of the heart, the injury to which would be expected to alter the electrocardiogram in the opposite directions, is much more likely to occur in massive infarcts than in small ones. In connection with this, it is well to point out that statistical studies have repeatedly shown that myocardial infarction which produces atypical patterns in the electrocardiogram offers a poorer prognosis than that in which typical patterns are present.⁵ Findings reported here may be considered an anatomic confirmation of this observation.

The practical implications of the observations presented in this report are obvious. Not only have no characteristic features of massive myocardial infarction been demonstrated, but it was shown that massive myocardial infarcts may be masked by a mild onset, absence of alarming signs, low grade constitutional reactions and equivocal laboratory and electrocardiographic findings. Symptoms of massive myocardial infarction may be so benign that doubt may even exist as to whether myocardial infarction has occurred at all in a patient with coronary artery disease.

SUMMARY AND CONCLUSIONS

A series of 28 cases of recent massive myocardial infarction found at autopsy was studied and the symptomatology, clinical course and laboratory and electrocardiographic findings presented.

The initial attack, the effects on the circulation and the constitutional reactions of acute myocardial infarction were not of uniform severity in this series. The predominance of mild and moderately severe clinical manifestations over extremely severe ones in proved cases of massive myocardial infarction suggests that there is no close correlation between the clinical picture and the anatomic changes. In spite of severe damage to the myocardium, several patients showed no evidence of serious circu-

5 (a) Barnes, A. R. Electrocardiogram in Myocardial Infarction. A Review of One Hundred and Seven Clinical Cases and One Hundred and Eight Cases Proved at Necropsy, *Arch Int Med* **55** 457 (March) 1935. (b) Rosenbaum, F. F., and Levine, S. A. Prognostic Value of Various Clinical and Electrocardiographic Features of Acute Myocardial Infarction. I. Immediate Prognosis, *ibid* **68** 913 (Nov.) 1941. (c) Woods, R. M., and Barnes, A. R. Factors Influencing Immediate Mortality After Acute Coronary Occlusion, *Am Heart J* **24** 4 (July) 1942.

latory insufficiency and presumably would have recovered had they not succumbed to secondary complications which developed in the course of acute myocardial infarction

Four lead electrocardiographic studies were not appreciably helpful in the diagnosis of massive myocardial infarction. Atypical patterns occurred in the majority of cases, and in some of them only minor deviations from normal were present.

The practical significance of these findings lies in the demonstration of the fact that massive myocardial infarction may cause benign clinical symptoms, suggesting only minor damage to the myocardium, or may even make the presence of a recent infarct questionable.

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PRIMARY MALIGNANT DISEASE OF THE SMALL BOWEL

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PRIMARY malignant disease of the small bowel is comparatively rare. As Morison¹ has stated, "For the area exposed, the small intestine enjoys as great an immunity from new growth as any part of the body." During the past few years, this condition has aroused increasing interest. The chief difficulty has been early diagnosis, but with the better technics now available for the roentgenologic investigation of the small intestine, its presence can be demonstrated sufficiently early to offer hope of successful surgical intervention. Awareness of the possibility remains, however, the prime necessity for its recognition and offers a challenge for early diagnosis. The present communication is a report of 15 cases encountered at City Hospital, Welfare Island, and 2 cases from other sources. They are separated into three groups, i.e., cases of carcinoma, cases of carcinoid or argentaffinoma and cases of lymphosarcoma, because of the differences in pathologic and clinical features. Carcinoma primary in the papilla or ampulla of Vater is excluded. The term lymphosarcoma is used to include malignant lymphocytoma and reticulum cell sarcoma. The data on the cases are summarized in table 1.

Tumors of the small bowel are most frequently benign.² Of the malignant tumors, carcinoma is usually believed to be more common than

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1 Morison, J. E. *Brit J Surg* **29** 139-153, 1941.

2 (a) Raiford, T. S. Tumors of Small Intestine, *Arch Surg* **25** 122-177 (July), 321-355 (Aug.) 1932. (b) Good, C. A. Tumefactive Lesions of Small Intestine, *JAMA* **117** 923-926 (Sept. 13) 1941. (c) Cohn, S., Landy, J. A., and Richter, M. Tumors of Small Intestine, *Arch Surg* **39** 647-666 (Oct.) 1939.

sarcoma,³ although some observers⁴ have found sarcoma to be more frequent. The argentaffinomas occupy a place in between the other types.⁵ They are all comparatively rare and comprise about 0.025 per cent of all cancers.⁶ The late statistics are given in table 2.

Carcinoma of the small bowel comprises about 3 per cent of gastrointestinal carcinomas and is much less common than carcinoma of the large bowel.⁷ Lieber and Stewart⁸ accepted 35 cases of suprapapillary carcinoma as authentic and 12 as probable. Ruden⁹ increased the number to 59. Felsen and Wolarsky¹⁰ collected 47 cases of infrapapillary duodenal lesion, including 1 of their own. It is more difficult to estimate the number of lesions involving the second part of the duodenum because frequently a clear distinction is not made between primary and secondary lesions. Up to 1943, less than 300 cases of carcinoma of the small bowel had been reported.¹¹ To these, 64 can be added,¹² including the present series. The cases of Nelson,¹³ Cohn¹⁴ and Child¹⁵ are questionable. These data suggest that an actual increase is occurring in the incidence of carcinoma of the small bowel. It is

3 (a) Warren, R. F. *Canad. M. A. J.* **51**: 451-457, 1944. (b) Shallow, T. A., Eger, S. A., and Carty, J. B. *Am. J. Surg.* **69**: 372-383, 1945. (c) Swenson, P. C. *Rev. Gastroenterol.* **10**: 77-91, 1943. (d) Cameron, A. L. *Ann. Surg.* **108**: 203-220, 1938. (e) Medinger, F. G. *Surg., Gynec. & Obst.* **69**: 299-305, 1939. (f) Fraser, K. *Brit. J. Surg.* **32**: 479, 1945. (g) Good.^{2b}

4 Mayo, C. W., and Nettrour, W. S. *Surg., Gynec. & Obst.* **65**: 303-309, 1937. Raiford.^{2a}

5 (a) Horsley, J. S. *Carcinoma of Jejunum and of Ileum*, *J. A. M. A.* **117**: 2119-2123 (Dec. 20) 1941. (b) Swenson.^{3c} Cameron.^{3d}

6 Mateer, J. G., and Hartman, F. W. *Primary Carcinoma of Duodenum: Clinical and Pathologic Aspects, with Differential Diagnosis*, *J. A. M. A.* **99**: 1853-1859 (Nov. 26) 1932.

7 Howard, J. W. *Am. J. M. Sc.* **206**: 735-745, 1943. Mayo and Nettrour.⁴

8 Stewart, H. L., and Lieber, M. M. *Carcinoma of Suprapapillary Portion of Duodenum*, *Arch. Surg.* **35**: 99-129 (July) 1937.

9 Ruden, S. J. *Primary Carcinoma of Duodenal Bulb*, *Arch. Path.* **43**: 616-619 (June) 1947.

10 Felsen, J., and Wolarsky, W. *Primary Infrapapillary Adenocarcinoma of Duodenum*, *Arch. Path.* **36**: 428-431 (Oct.) 1943.

11 McDougal, W. J. *Am. J. Surg.* **66**: 119-122, 1944.

12 (a) Bottsford, J. W., and Seibel, R. E. *New England J. Med.* **236**: 683-694, 1947. (b) Emmet, J. M., and Dreyfuss, M. L. *Ann. Surg.* **123**: 859-865, 1946. (c) Ehrlich, J. C., and Hunter, O. B. *Surg., Gynec. & Obst.* **85**: 98-106, 1947. (d) Shallow, T. A., Eger, S. A., and Carty, J. B. *Surgery* **16**: 939-946, 1944. (e) Mulligan, R. M. *Adenocarcinoma of Jejunum Associated with Hyperplasia of Parathyroid Glands and Generalized Osteoporosis*, *Arch. Path.* **40**: 182-186 (Sept.) 1945. (f) Warren.^{3a} (g) Shallow.^{3b} (h) Swenson.^{3c} (i) Howard.⁷

13 Nelson, H. *Minnesota Med.* **28**: 396-398, 1945.

14 Cohn, I. *Ann. Surg.* **119**: 342-350, 1944.

15 Child, C. G., III. *Ann. Surg.* **118**: 838-843, 1943.

TABLE 1—*Clinical and Pathologic Data in Cases Observed*

Case No	Clinical Features	Pathologic Process	Metastasis
1*	W M, 34 Onset with substernal epigastric and general abdominal pain and constipation, sudden episode in 6 months of severe epigastric pain, persistent vomiting subsequently weight loss, melena, slight anemia, marked epigastric tenderness, stenotic lesion of duodenum on fluoroscopy, total duration 1 year	Suprapapillary carcinoma	None
2†	W F, 70 Onset with moderately severe upper abdominal pain, similar attack in 2 months, with mild jaundice, third attack 1 year later, with palpable mass resection living 1 year later, clinical evidence of metastasis	Carcinoma of the mesial wall of the second part of the duodenum	Regional lymphatic vessels invasion of contiguous pancreatic region
3	W M, 63 Two years of postprandial pain and late jaundice vomiting, clay colored stools weight loss deep jaundice, moderate anemia, narrowed duodenum in roentgenograms, cholecystojejunostomy recurrence of jaundice death autopsy total duration 2 years, 3 months	Intrapapillary carcinoma	Regional lymphatic vessels invasion of contiguous pancreatic region
4	W M, 70 Ten year history of ulcer, one period of upper abdominal and retrosternal pain examination noncontributory, 5½ years later history of melena for 3 years abdominal pain for 3 months loss of weight alternating diarrhea and constipation, moderate abdominal rigidity, right upper quadrant tenderness deformed duodenum, pulmonary tuberculosis death from pulmonary and iliac tuberculosis autopsy	Intrapapillary carcinoma	Regional lymphatic vessels invasion of contiguous pancreatic region
5‡	W M, 46 Onset with listlessness for 1½ year, then increased listlessness severe anemia upper abdominal pain, slight weight loss, deformity at ligament of Treitz and signs of slight retention in roentgenograms, resection, living 1 year later apparently free of disease	Carcinoma of the jejunum near the ligament of Treitz	None
6	W F, 77 Admitted in extremis no history of gastrointestinal disturbance, death in 4½ hours from acute pneumonia and endocarditis autopsy small carcinoma of hepatic flexure without metastasis	Carcinoma of upper jejunal area	None
7	W M, 68 Sudden onset of severe periumbilical pain, vomiting, constipation several years of burning epigastric pain, three years previously 6 weeks of severe constipation followed by progressive weight loss, palpable mass, midjejunal obstruction, resection further course unknown	Carcinoma of middle jejunal area	?
8	W F, 64 Sudden attack of upper abdominal pain slight icterus slight abdominal distention, spasticity rebound tenderness, anemia, improvement in 3 weeks recurring attacks of abdominal pain and vomiting for 7 months, occult blood in stool marked weight loss lower jejunal obstruction and retention resection recurrence of obstruction, metastasis on laparotomy, death, no autopsy, total duration 3 years	Carcinoma of lower jejunal area	Mesentery peritoneum, liver
9	W F, 72 Two years of epigastric distress aggravated by meals, death autopsy total duration, 2 years	Adenocarcinoma of the upper ileum	Mesentery peritoneum
10	W F, 72 Cardiac disease, no gastrointestinal disturbance	Multiple adenocarcinomas of the upper ileum and the jejunum	Mesenteric nodes, peritoneum

Case No	Clinical Features	Pathologic Process	Metastasis
11	W M, 62 Cardiac disease, no gastrointestinal disturbance	Adenoma of the middle ileum	Mesentery, liver
12	W M, 44 Episodes of severe abdominal pain for 4 years, more severe and frequent for 1 month, no relation to meals, signs of perforation, operation, perforation of jejunum, general peritonitis, death, autopsy, total duration, 4 years	Multiple argentaffinomas of the lower ileum (?)	Cecal and celiac lymphatic nodes, peritoneum liver
13	B F, 51 "Gas pains" and diarrhea for 4 weeks rectosigmoid obstruction resection of ileum and colonotomy, rectosigmoid obstruction from lymphoplastic venereum	Argentaffinoma of the ileum	None
14	W M, 58 Cardiac and prostatic disease no gastrointestinal disturbance	Argentaffinoma of the ileum	None
15 ¹	W F, 16 Admitted in extremis, death in 8 hours, five year history of recurrent vomiting and diarrhea, later weight loss, autopsy, total duration, 5 years	Diffuse lymphosarcoma of the duodenum and jejunum	None
16	W F, 60 Four year history of weakness, vomiting, distention and intolerance to fats, cholecystectomy two years later, with short free period, recurrence of nausea and vomiting, epigastric pain 1½ years, gradual weight loss, acute episode of perforation, laparotomy—perforation through tumor mass, resection, death, no autopsy, total duration, 1 year	Lymphosarcoma of the jejunum	?
17	Chinese M, 15 Acute onset of constant abdominal pain, vomiting, tarry stools, signs of peritonitis, operation, perforated jejunum, peritoneal metastasis, death no autopsy	Lymphosarcoma of the jejunum	Peritoneum

*Previously reported by Lisa and others (case 2, J Lab & Clin Med 20 150, 1934)

†Dr Russell H. Patterson gave us permission to include this case

‡From the private practice of one of the authors (D S L)

§Previously reported by Likely and Lisa (Am J Digest Dis & Nutrition 6 113, 1939 [case 2]) as a case of granulomatous tumor Reexamination indicated that this diagnosis was incorrect

TABLE 2—Statistical Incidence of Primary Malignant Growths of the Small Bowel

Authors	Period, Yr	Source	Carcinomas	Adenofibromas	Lymphosarcomas*
Cameron ^{3d}		200 jejunal and ileal malignant growths	109	13	(78)
Morrison ¹	10 10	13 139 autopsies and operations Clinical records	4 2	2 1	4 (2)
Swenson ^{3c}	-	50 malignant growths of the small bowel	22	4	15
Warren ^{3a}	17	- - -	17	4	2
Bottsford and Seibel ^{12a}	34	Autopsies and operations	18	16	13
Likely and others	27	6 226 autopsies 23 776 surgical procedures others	4 2 2	5 1 -	1 2
Medinger ^{3c}	12	1 156 autopsies 41,000 operations	16	--	0
Morrison and Donath ^{41a}		25,631 autopsies and operations 28 390 admissions	10	-	2
Fraser ^{3f}	10	22 970 operations 2,674 autopsies	6	--	(7)
Shallow and others ^{3b}		-	186	-	(83)
Emmet and Dreyfuss ^{12b}	10	-	11	--	(7)
Swan J M M Times New York 74 46 52 and 105 112 1946		-----	258	-	13
Ehrlich and Hunter ^{12c}		441 malignant growths of the gastrointestinal tract	9	--	2
Horsley ³	9	Jejunum and ileum	243	141	-
Mayo and Nettrour		-	76		--
Howard ⁷	13	10 340 autopsies on patients with carcinoma 1 650 autopsies	152 5	-- --	-
O Donoghue and others ^{45a}	14	16 318 autopsies	7		--
Boman ⁵⁰		230 000 admissions	7	-	
Ficarra and Marshall ²⁷	30		29	--	-
Porter and Whelan ³³	28	-		9	-
Dockerty and Ashburn ³²	37	-		30	
Chont L K Radiology 36 86 97 1941		2 252 autopsies 20 603 operations	-	-	3
Sugarbaker and Craver ^{51a}	20	196 lymphosarcomas			4
Menne and others ³⁹	-	11 416 autopsies 38 076 operations		-	1
Ritter and Shaffer ^{56a}	13	-		-	5
Frank and others ²³		102 lymphosarcomas of the small large bowels	-	--	69
Usher and Dixon ^{21a}		50 sarcomas of the small and large bowels	--	--	19
Kock ^{24b}	41	Operative cases	-	--	7
Cutler and others ^{21b}	10	- - - -	-	--	2

*Figures in parentheses include sarcomas other than the lymphomatous type

interesting to note that in our series, covering a period of twenty-seven years, 5 of the 6 cases were observed in the last six years

Argentaffinoma of the small intestine has been reported with increasing frequency since the classic contribution of Forbus¹⁶ in 1925 Gaspar¹⁷ collected about 70 cases, other observers¹⁸ increased the number to 332 by 1944 About 33 more have been reported since then,¹⁹ to which can be added the present series Probably, as Horsley⁵ has stated, they are more frequent than commonly believed

Lymphosarcoma of the small bowel, in contrast to carcinoma, is more frequent than that of the large bowel²⁰, only a few reports²¹ show the reverse Its true incidence is difficult to estimate because of insufficient or obscure data in the reports and of conflicting figures²² Frank and others²³ found 361 cases of intestinal lymphosarcoma in the literature up to August 1942 Of the 102 in which a histologic diagnosis was made, 69 were cases of lymphosarcoma of the small intestine Since then 80 cases, including the present series, have been reported²⁴ In

16 Forbus, W D Bull Johns Hopkins Hosp 37 130-153, 1925

17 Gaspar, I Am J Path 6 515-524, 1930

18 (a) Ariel, I M Argentaffin (Carcinoid) Tumors of Small Intestine Report of Eleven Cases and Review of Literature, Arch Path 27 25-52 (Jan) 1939 (b) Dangremond, G Am J Clin Path 12 223-231, 1942 (c) Ritchie, G, and Stafford, W T Argentaffin Tumors of Gastrointestinal Tract, Arch Path 38 123-127 (Sept) 1944

19 (a) Bonar, A A Brit M J 1 391-392, 1946 (b) Watz, C E Minnesota Med 28 558-559, 1945 (c) Blumgren, J E ibid 27 620-623, 1944 (d) Korkosz, A Gastroenterology 1 961-964, 1943 (e) Malignant Carcinoid of Ileum, Cabot Case 30241, New England J Med 230 739-742, 1944 (f) McLeod, C E Am J Clin Path 14 301-303 1944 (g) Stevenson, W O, and Blanchard, A J Canad M A J 51 259-260, 1944 (h) Betancourt, P I, and Vidauretta, Z M Arch cubanos cancerol 3 113-124 1944 (i) Reynolds, R P, and Cantor, M O Am J Surg 71 705-709, 1946 (j) McNeely, R D G, and Jones, W N Gastroenterology 6 443-448, 1946 (k) Swenson^{3c} (l) Bottsford and Seibel^{12a}

20 (a) Windt, G V Rev Policlin Caracas 14 277-285, 1945 (b) Ulmann, A, and Abeshouse, B S Am Surg 95 878-915, 1932 (c) Raiford^{2a} (d) Warren^{3a} (e) Shallow, Eger and Carty^{3b} (f) Ehrlich and Hunter^{12c} (g) Morison¹

21 (a) Usher, F C, and Dixon, C F Gastroenterology 1 160-178, 1943 (b) Cutler, G D, Stark, R B, and Scott, H W New England J Med 232 665-670, 1945

22 (a) Benjamin, E L and Christopher F Am J Clin Path 10 408-413, 1940 (b) Charache, H Am J Surg 59 601, 1943

23 Frank, L W, Miller, A J, and Bell, J C Ann Surg 115 544-565, 1942

24 (a) Borden, D L, and Taylor, F D Mil Surgeon 92 255-257, 1943 (b) Dinsmore R S, and Ancona, V C Cleveland Clin Quart 11 77-79, 1944 (c) Sanguily, J Arch cubanos cancerol 4 170-176, 1945 (d) Berman, H, and Mainella, F Am J Surg 70 121-125, 1945 (e) Moreton, R D Texas State J Med 41 458-464, 1946 (f) Mascheroni, H A Reussi, C, and Clerici, L E Rev Asoc med argent 60 330-333, 1946 (g) Alsup, F F Hawaii M J 5

addition 3 probable cases have been reported²⁵ Mena's case²⁶ may be one of an inflammatory lesion There are probably about 200 authentic cases in the literature

The site of predilection of carcinoma, argentaffinoma and lymphosarcoma, differs In cases of carcinoma, each segment, i e, duodenum,²⁷ jejunum²⁸ and ileum,²⁹ has been ranked first Other observers³⁰ found no particular susceptibility of any segment The statement of Morison,¹ however, appears justified "For the area at risk, the literature does suggest that the highest incidence of carcinomata of the small intestine is in the duodenum" In the duodenum, the second portion is most likely to be affected³⁰ The ileum is the favorite location for argentaffinoma and lymphosarcoma Including the 69 cases of Frank and others²⁸ and the more recent cases in which the site is given, 15 cases of duodenal, 31 cases of jejunal and 68 cases of ileal lymphosarcoma have occurred In 10 cases there was a multiple origin

Carcinoma of the small bowel usually occurs in the form of a single lesion, tends to be stenotic, encircles the lumen and involves short segments In some cases it is polypoid, fungating or pedunculated Multiple carcinomas are rare Histologically, it usually shows gland formation, scirrhous reaction and papillation Adenocanthoma is rare,³¹ as is colloid carcinoma Causal relation to duodenal ulcer is doubtful⁸

Carcinoids are usually small submucous masses, firm in consistence, extending toward the mucosa, which frequently remains intact, and growing outward into the mesentery Gross ulceration is uncommon, although small ulcers can be demonstrated frequently in the larger tumors on microscopic examination³² They occasionally are pedunculated They tend to involve only a portion of the wall and do not

197-198, 1946 (*h*) Svein, H J, and Rivers, A B *Am J Digest Dis* 9 45-47, 1942 (*i*) Fritzsche, R *Schweiz med Wchnschr* 73 442-445, 1943 (*j*) Wybert, A, and Rodrigues, R V *Rev Asoc méd argent* 55 443-446, 1941 (*k*) Kock, W *Acta chir Scandinav* 89 37-67, 1943 (*l*) Warren^{3a} (*m*) Swenson^{3c} (*n*) Bottsford and Seibel^{12a} (*o*) Ehrlich and Hunter^{12c} (*p*) Footnote 21

25 Montel, M G *Lyon chir* 37 339-340, 1942 Colesanti, G *Gazz internaz med-chir* 47 315-320, 1937 Windt^{20a}

26 Mena, R I *Rev med de Chile* 71 800-803, 1943

27 Ficarra, B J, and Marshall, S F *S Clin North America* 25 713-718, 1945 Raiford^{2a}

28 Swenson^{3c} Mayo and Nettrour⁴

29 Bottsford and Seibel^{12a} Fraser^{3f}

30 Berger, L, and Koppelman, H *Ann Surg* 116 738-750, 1942

31 Lieber, M M, Stewart, H L, and Morgan, D R Adenosquamous Carcinoma of Peripapillary Portion of Duodenum, *Arch Surg* 40 988-996 (May) 1940

32 Dockerty M B, and Ashburn, F S Carcinoid Tumors (So-Called) of Ileum Report of Thirteen Cases in Which There Was Metastasis, *Arch Surg* 47 221-246 (Sept) 1943

encircle the circumference. A favorite location is at or near the mesenteric reflexion. The lumen of the intestine is slightly encroached on by the tumor but mainly deformed by angulation caused by growth into the mesentery. On section, the color is frequently yellow or gray, with yellow foci. Many times they are multiple, and they may occur in groups. The rate of growth is slow. The origin of the carcinoid is considered to be the Kulschitzky cells of Lieberkuhn's glands. They form small homogeneous cell masses separated by fibrous septums. The cells are small, opaque and finely granular, have obscure borders and are chromophilic and argentophilic. The peripheral cells tend to be in palisade formation. Occasionally there are glands. The nuclei are round or oval and stain deeply. In morphologic pattern, carcinoids closely resemble basal cell carcinoma of the skin.

Lymphosarcoma appears to have a focal origin in lymphatic tissue³³ and may develop as the small cell type, malignant lymphocytoma, or the large cell type, reticulum cell sarcoma. In the small intestine it arises from the lymphatic tissue of the mucosa and submucosa. The tendency is toward diffuse invasion and outward growth into the wall and mesentery and longitudinally along the long axis. Usually it involves the entire circumference and a longer segment than that involved in carcinoma. It is more likely to cause dilatation of the lumen than stenosis, producing an aneurysmal small mass. Sometimes it is constricting and fungating. Ulceration is frequent. The tissue is homogeneous, fairly firm and gray. The tumor may be multicentric in origin. According to Cameron,³⁴ one twelfth are of this nature.

Regional metastasis in carcinoma is said to occur early.³⁴ Howard⁷ claimed that it was late, and Raiford^{2a} found metastasis in only 25 per cent of his cases. Contiguity invasion of the pancreas is stated to be rare.¹ In our experience it has not been uncommon in duodenal lesions, and Howard's experience is similar. Distant metastasis is late.

Carcinoids of the small bowel have been classed as benign tumors,³⁵ but their tendency to metastasize justifies their inclusion among the malignant growths. Porter and Whelan³⁶ have shown that carcinoids of the gastrointestinal tract, other than appendical, have a definite tendency to metastasize. Dockerty and Ashburn³² reported metastasis in 43 per cent of their cases. Usually it occurs only in the draining lymphatic vessels, but the liver is a fairly common site. Widespread

33 Stout, A. P. Is Lymphosarcoma Curable? *J. A. M. A.* 118:968-970 (March 21) 1942. Ulmann and Abeshouse^{20b}

34 Rankin, F. W., in discussion on Horsley⁵ Fraser^{2f} Mayo and Nettrour⁴ Bottsford and Seibel^{12a}

35 Morison¹ Raiford^{2a} Cohn^{2c} Forbus¹⁸

36 Porter, J. E., and Whelan, C. S. *Am. J. Cancer* 36:343-358, 1939

metastasis³⁷ is uncommon. The metastasis has the same slow growth as the primary lesion.

In lymphosarcoma, lymphatic metastasis apparently occurs early,³⁸ although Raiford^{2a} stated that it occurs less readily than in carcinoma. Hematogenous spread is uncommon.³⁹

Persons with carcinoma and lymphosarcoma of the small intestine are predominantly male, there is no sex difference for carcinoids. The average age at which carcinoma occurs is the fifth decade. Carcinoids tend to occur among older persons. Fifty per cent of the cases of lymphosarcoma involve persons between 30 and 60 years of age²³ and 10 per cent involve infants and children.⁴⁰

The symptoms of the three types of malignant growths of the small intestine have several features in common and certain differences. They are somewhat dependent on the site of the lesion, may be acute or chronic in onset and may be present for a variable period. The most characteristic symptom complex is that of intermittent obstruction.⁴¹ With high tumors, vomiting occurs early.⁴¹ In suprapapillary carcinoma, acute onset is common and vomiting prominent.⁴² The vomitus usually contains blood, free hydrochloric acid and gastric enzymes. The lesions of the second portion of the duodenum tend to give the same signs, with mild transient jaundice. In infrapapillary lesions there are obstructive symptoms, gastric upsets and vomitus which contains blood, bile, hydrochloric acid and gastric and pancreatic enzymes. Gastric upsets are less noticeable and more transient^{3b} and sometimes are manifested only by unexplained mild nausea⁷ when the lesions are lower in the tract.

Anemia is common in cases of carcinoma and sarcoma and extremely unusual in cases of carcinoid. Massive hemorrhage is not frequent, although the stool usually contains occult blood, except when carcinoid is present. Easy fatigability is usually associated with the anemia.

Pain is almost invariable in sarcoma,⁴³ and is common in carcinoma, and it is usually cramplike during periods of obstruction.

37 Porter³⁰ Watz^{10b}

38 Ulmann and Abeshouse^{20b} Usher and Dixon^{21a}

39 Meune, F. R., Mason, D. G., and Johnston, R. Lymphosarcoma of Intestine. Report of Two Cases, *Arch Surg* **45** 945-956 (Dec.) 1942

40 Cameron^{3d} Frank, Miller and Bell²³

41 (a) Morrison, W. A., and Donath, D. *California & West Med* **55** 235-237, 1941. (b) Swenson^{3c} Bottsford and Seibel^{12a} Emmet and Drevfuss^{12b} Frank, Miller and Bell²³

42 Cohn¹⁴ Berger and Koppelman⁷⁰

Change of bowel habits is usually manifested by constipation, apparently coinciding with obstruction. Alternating diarrhea and constipation seem to be late and do not occur frequently.

Loss of weight occurs early in sarcoma, is usually late in carcinoma and is absent in carcinoid.

Palpable tumor is more common when the lesions are of the lower segments. It is frequent in sarcoma⁴³ and in jejunal and ileal carcinoma and occasionally present in carcinoid.

Intussusception, usually due to benign lesions,⁴⁴ is frequent in sarcoma and uncommon in the other two malignant growths. It may occur with pedunculated tumors.⁴⁵ Perforation is uncommon but occasionally occurs.⁴⁶ Pellagrous^{19j} and spruelike syndromes⁴⁷ are rare manifestations.

Cases of carcinoma⁴⁸ and sarcoma²¹ in which the patients are symptom free are uncommon. Silent carcinoids are more frequent.⁴⁹

The prognosis is considered poor in cases of carcinoma⁵⁰ and sarcoma⁵¹, it is good in cases of carcinoid.⁵² Cameron^{3a} stated that the five year survival rate in the first two types is less than 5 per cent. Of the carcinomas, jejunal and ileal lesions carry a more favorable prognosis than duodenal lesions.⁵³ The sarcomas carry a more favorable prognosis⁵⁴ than the carcinomas. The prognosis depends somewhat on the presence or absence of metastasis in carcinoma and sarcoma⁵⁵ but not in carcinoids. The slow growth of carcinoids does not tend to shorten life. However, there have been reported several cases in which there was a long survival even after operation for more malignant tumors.⁵⁶ Most of these have been reported in the later years, which suggests that the prognosis in the future may not be so hopeless as early experience denoted.

43 Bottsford and Seibel^{12a} Ulmann and Abeshouse^{20b}

44 Fiske, F. A. *Ann Surg* **106** 221-229, 1937

45 (a) O'Donoghue, J. B., Lichtenstein, M. E., and Jacobs, M. B. *Am J Surg* **63** 382-387, 1944 (b) Black, B. M. *Proc. Staff Meet., Mayo Clin* **19** 142-146, 1944 Korkosz^{10d}

46 Fraser^{3f} Kock^{21k} Korkosz^{10d} McLeod^{10f}

47 Swenson^{3c} Fritzsche²¹ⁱ

48 Swenson^{3c} Ruden⁹ Felson and Wolarsky¹⁰

49 Bottsford and Seibel^{12a} Porter and Whelan²⁰ Ariel^{18a} Dangremond^{18b}

50 (a) Boman, P. G. *Ann Int Med* **20** 779-788, 1944 (b) Raiford²¹ (c) Warren²¹ (d) Bottsford and Seibel^{12a} (e) Black^{45b}

51 Sugarbaker, E. D., and Craver, L. F. *Lymphosarcoma. Study of One Hundred and Ninety-Six Cases with Biopsy*, *JAMA* **115** 17-23, (July 6), 112-117 (July 13) 1940 (b) Cameron^{3d} (c) Usher and Dixon²¹ⁱ (d) Kock^{21k}

52 Warren²¹ Ariel^{18a} Dockerty³² Footnote^{10e}

53 Shallow, Eger and Carty^{3b} Medinger^{3e}

54 Shallow, Eger and Carty^{3b} Ulmann and Abeshouse^{20b}

55 Howard² Rankin³⁴

Roentgenologic examination is a most valuable procedure in the diagnosis of malignant growths of the small bowel. The criteria are the same as those used for the diagnosis of tumors in the large bowel⁵⁷ and give evidence of the gross nature of the lesion⁵⁸. It is worth noting, however, that growths of equal size in the colon produce a more definite type of picture. Plain roentgenograms sometimes prove of value if they indicate obstruction^{12a}.

Therapy is radical resection, with removal of draining lymph nodes. For argentaffinomas, this is indicated even in the presence of metastasis to the liver. Postoperative irradiation has been used in some cases of lymphosarcoma and not in others, with identical long survival periods.

SUMMARY AND CONCLUSIONS

Seventeen cases of malignant growth of the small bowel are reported, and the recent literature is reviewed. They are of uncommon occurrence. Certain clinical features suggest the possibility of their presence. Intermittent obstruction is a common manifestation. In some cases the presenting symptom is mild unexplained nausea. In the presence of anemia of gastrointestinal origin for which no adequate explanation is found on examination of the stomach and large bowel the small bowel should be thoroughly investigated. The prognosis is usually considered poor in cases of carcinoma and lymphosarcoma and good in cases of argentaffinoma. The more recent literature suggests that the prognosis may depend largely on early diagnosis rather than on the type of tumor, particularly in reference to carcinoma and lymphosarcoma. Roentgenologic studies are most valuable. The therapy is radical resection. Awareness of the possibility of the existence of the condition remains the prime necessity for early diagnosis.

56 (a) Ritter, H. H., and Shaffer, J. M. *Am J Surg* 55 611-612, 1942
 (b) Horsley⁶ (c) O'Donoghue^{45a} (d) Shallow, Eger and Carty^{5b} (e) Swenson^{3c}
 (f) Morison¹ (g) Fraser^{3f} (h) Medinger^{3e} (i) Ulmann and Abeshouse^{20b} (j)
 Berman and Mainella^{24d} (k) Charache^{22b} (l) Alsup^{21g} (m) Warren^{3a} (n) Usher
 and Dixon^{23a}

57 Good, C. A., and McCarthy, W. E. *Proc Staff Meet, Mayo Clin* 17
 20-22, 1942. Good^{2b}

58 Weber, H. M., and Kirklin, B. R. *Am J Roentgenol* 47 243-253 1942

STREPTOMYCIN

Report of Its Clinical Effects in Forty-Four Patients Treated for Various Infections of the Respiratory Tract

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UP TO THIS writing, 44 cases of nontuberculous infections of the respiratory tract in which the patient was treated with streptomycin have been fully studied in Army hospitals. The number of cases is small because relatively few pleuropulmonary infections are caused by organisms which do not respond satisfactorily to the sulfonamide compounds and penicillin.

The sulfonamide compounds have a pronounced effect on bacterial pulmonary infections caused by *Diplococcus pneumoniae* (*Pneumococcus*) except type III and the hemolytic streptococci. *Hemophilus influenzae*, *Klebsiella pneumoniae* and *Staphylococcus aureus* infections are less strikingly influenced. One of the chief advantages of the sulfonamide compounds is that they are effective when administered orally. The common types of pulmonary infection which respond favorably to the sulfonamide compounds improve even more dramatically when penicillin is administered. The repeated and wearying injections necessary when this antibiotic is used are more than compensated for by the greater efficacy and relative freedom from untoward reactions. This objection may be overcome by the suggested twice daily injections of procaine-penicillin and penicillin-oil mixtures. Penicillin is effective when it is introduced into the thoracic cavity by direct injection or into the tracheobronchial tree by nebulization, either method making it possible to bring the drug into actual contact with the site of infection. An additional advantage of penicillin therapy is that penicillin is not inactivated by pus.

Notable among the nontuberculous infections of the respiratory tract which do not respond dramatically to the sulfonamide compounds and penicillin are those caused by *H. influenzae* and *Hemophilus pertussis*, *K. pneumoniae*, and *Pasteurella tularensis*. An even smaller category con-

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sists of the occasional infections caused by other organisms refractory to penicillin before therapy but sensitive to streptomycin

REVIEW OF LITERATURE

The literature on the streptomycin therapy of nontuberculous infections of the respiratory tract is small. Case reports for the most part dealing with single experiences,¹ indicated that lobar pneumonia caused by *K. pneumoniae* and bronchopneumonia caused by *H. influenzae* usually responded to streptomycin therapy, although they had not responded to penicillin or the sulfonamide compounds. Streptomycin was promptly established as the accepted drug in the treatment of pleuropulmonary tularemia.² The only published clinical experience with streptomycin in pertussis at this writing is that of Coffey and Levy.³ Four children in whom pneumonia occurred during pertussis were treated with streptomycin, recovery followed this therapy. The patients were aged 7 weeks, 6 months, 3 years and 6 years, respectively. In 2 cases penicillin was administered prior to streptomycin, without clinical improvement. Streptomycin was given intramuscularly in doses of 100 to 200 mg every three hours. Two premature twins, 7 weeks of age, with pertussis pneumonitis died after having shown an initial favorable response to streptomycin.

The report of the National Research Council⁴ includes 44 cases of acute or chronic pulmonary infection due to a variety of organisms. None

1 Durant, T. M., Sokalchuk, A. J., Norris, C. M., and Brown, C. L. Streptomycin Therapy in Hemophilus Influenzae Pulmonary Infections, *J. A. M. A.* **131** 194-196 (May 18) 1946. DeBakey, M. E., and Pulaski, E. J. Analysis of Experience with Streptomycin in United States Army Hospitals. Preliminary Report, *Surgery* **20** 749-760 (Dec.) 1946. Bishop, C. A., and Rasmussen, R. F. Klebsiella Pneumonia Treated with Streptomycin, *J. A. M. A.* **131** 821-822 (July 6) 1946. Learner, N., and Minnich, W. R. Friedlander Pneumonia Treated with Streptomycin. Report of Case with Prompt Recovery, *Ann. Int. Med.* **25** 516-520 (Sept.) 1946. Geier, F. M. Case of Friedlander's Bacillus Pneumonia Treated with Streptomycin, *Permanent Found. M. Bull.* **4** 159-163 (Nov.) 1946. Miller, B. W., Orris, H. W., and Taus, H. H. Friedlander's Pneumonia in Infancy, *J. Pediat.* **31** 521 (Nov.) 1947. Davis, J. P., Cheek, K. M., and Harrell, G. T., Jr. Friedlander Pneumonia with Bacteremia Successfully Treated with Streptomycin. Report of a Case, *North Carolina M. J.* **8** 767 (Dec.) 1947. Bulgrin, J. G. Unusual Friedlander's Bacillus Pneumonia Associated with Septicemia, *Radiology* **50** 526-528 (April) 1948.

2 Foshay, L. Treatment of Tularemia with Streptomycin, *Am. J. Med.* **2** 467-473 (May) 1947. Hunt, J. S. Pleuropulmonary Tularemia. Observations on Twelve Cases Treated with Streptomycin, *Ann. Int. Med.* **26** 263-276 (Feb.) 1947. Pulaski, E. J., and Amspacher, W. H. Streptomycin Therapy of Tularemia in U. S. Army Hospitals, *Am. J. M. Sc.* **214** 144-147 (Aug.) 1947.

3 Coffey, J. D., and Levy, H. B. Streptomycin in the Treatment of Pertussis Pneumonia, *Mississippi Doctor* **25** 295 (Feb.) 1948.

4 Streptomycin in Treatment of Infections. Report of One Thousand Cases, Committee on Chemotherapeutics and Other Agents, National Research Council, *J. A. M. A.* **132** 4-11 (Sept. 7), 70-76 (Sept. 14) 1946.

of the patients had shown any effect of previous treatment with either the sulfonamide drugs or penicillin. In 17 cases the infection was due to Friedlander's bacilli. Streptomycin was extremely effective in those cases in which treatment was started early, but permanent benefits were few or transitory in the cases in which the disease process had been longer established. Three of 4 patients with *H. influenzae* infections recovered, and 1 died. Of 4 patients with gram-positive coccal infections, 3 were cured, and the fourth showed no improvement. The remaining 19 had various acute or chronic forms of infections with mixed gram-negative and gram-positive organisms, concerning which no conclusions were drawn.

Harris and co-workers⁵ also had beneficial results from streptomycin therapy in 3 cases of pneumonia due to *H. influenzae* and *K. pneumoniae*.

*Results of Streptomycin Therapy **

	Cases	Number in Which Results Were		
		Good	Doubtful	Poor
Pneumonia due to				
<i>Klebsiella pneumoniae</i> (Friedlander's bacillus)	6	6		--
<i>Hemophilus influenzae</i>	2	2		
<i>Pasteurella tularensis</i>	3	3		
Hemolytic streptococcus	1	1		
<i>Pneumococcus</i> type IX	1		1	
Pertussis with bronchopneumonia	2		2	
Pneumonia with agranulocytosis	1	1		
Primary atypical pneumonia	1			1
Asthma with chronic infection of the upper respiratory tract	3			3
Bronchitis	6		1	5
Bronchiectasis	6	2	1	3
Actinomycosis	1			1
Blastomycosis	1		1	
Monilliasis	1			1
Sarcoidosis	7			7
Hodgkin's disease	2			2
Total	44	15	6	23

*The average intramuscular dose was 0.25 Gm. given every three hours.
The average aerosol dose was 100 to 250 mg. dissolved in 1 to 2.5 cc. given four times a day.

In 3 cases of recurrent bronchopulmonary infection with a predominantly gram-negative flora the effects were less uniformly favorable. Drug fastness developing in the organisms not eradicated is advanced as one of the causes of the poor clinical result.

It is too early to speak of the relative value of streptomycin as used in chronic septic bronchiectasis, but current experience⁶ suggests that

5 Harris, H. W., Murray, R., Paine, T. F., and Finland, M. Streptomycin Treatment of Pulmonary Infections. Clinical and Bacteriologic Studies of Six Cases, *New England J. Med.* 236: 611-622 (April 24) 1947.

6 Olsen, A. M. Streptomycin Aerosol in Treatment of Chronic Bronchiectasis. Preliminary Report, Proc. Staff Meet., Mayo Clinic 21: 53-54 (Feb. 6) 1946, Nebulization Therapy in Bronchiectasis, *J. A. M. A.* 134: 947-953 (July 12) 1947. Kane, L. W., and Foley, G. E. Streptomycin Therapy in Fifty-Two Cases of Bacterial Infection, *New England J. Med.* 237: 531-540 (Oct. 9) 1947.

streptomycin-sensitive organisms can be reduced for a time, with change in the character and the volume of the sputum. Frequently the sputum becomes purulent after the drug has been withdrawn. Streptomycin is well tolerated when administered by the aerosol technique, whether used alone or in combination with penicillin. A few patients treated with streptomycin for empyema have shown varying responses, but details are meager in the few published reports.

In this communication we report the experiences which we have accumulated in treating pleuropulmonary infections with streptomycin in United States Army hospitals. The results of this therapy are listed in the table.

CLINICAL RESULTS

KLEBSIELLA PNEUMONIAL PNEUMONIA

CASE 1—A 51 year old white man, after a partial gastric resection for ulcer, had chills, fever (100 F) and pain in the chest on respiration. Signs of consolidation were present. In the sputum *K. pneumoniae* was predominant. On the second postoperative day, administration of streptomycin was started, 0.4 Gm being injected intramuscularly every four hours. This dosage was continued for nine and one-half days. Within twenty-four hours there were marked clinical improvement, reduction of sputum and lowering of temperature, with uncomplicated recovery ensuing.

CASE 2—A 29 year old soldier had chills and fever, his temperature rising to 104.5 F. He was treated for pneumococcal pneumonia, 50,000 units of penicillin was given every three hours, and 1 Gm of sulfadiazine every four hours, for fourteen days, without effect. At this time the sputum was reported to contain Friedlander's bacilli. Streptomycin therapy was begun, 0.2 Gm was injected intramuscularly every three hours for seven days. The patient responded after the first twelve hours of this therapy. His temperature subsided by lysis from 104.5 F to normal within six days. The pneumonia resolved without any evidence of abscess formation.

CASE 3—The patient was a 37 year old officer. Cyanosis and increasing signs of consolidation at the bases of both lungs developed over a five day period of sulfadiazine therapy, in the course of which this drug was given alone at the rate of 1 Gm every four hours, then combined with penicillin, 30,000 units every three hours. Type C Friedlander bacilli were isolated from the sputum. The temperature rose to 101.8 F daily. Streptomycin therapy was started on the sixth day, 0.5 Gm being given every four hours. Within thirty-six hours the patient's temperature had become normal and marked clinical improvement had occurred. After nine days of therapy, considerable asymptomatic residual fibrosis or unresolved pneumonia remained. This cleared spontaneously in about thirty days.

CASE 4—In a 36 year old soldier typical pneumonia involving the lower lobe of the left lung developed six days after inhalation anesthesia was induced for a surgical operation on the hand. His sputum contained type A Friedlander bacilli in great numbers. After four days of penicillin therapy, he showed clinical improvement but increasing consolidation. Streptomycin was then substituted for penicillin, 0.2 Gm being given every three hours for ten days. There was com-

plete disappearance of thoracic pain, sputum and fever, and the temperature fell to normal within forty-eight hours. Serial roentgenograms of the lungs showed a gradual clearing of the pneumonic process over a two week period.

CASE 5—A soldier aged 37 was admitted to the hospital with a one day history of severe shaking chills, high fever and a cough productive of bloody sputum. Physical examination showed an acutely ill, dyspneic patient with a temperature of 104.5 F and fine moist rales in the right lung field. Roentgenograms showed an area of consolidation radiating from the right hilus. Combined sulfadiazine and penicillin therapy was started. Two days later there were signs of

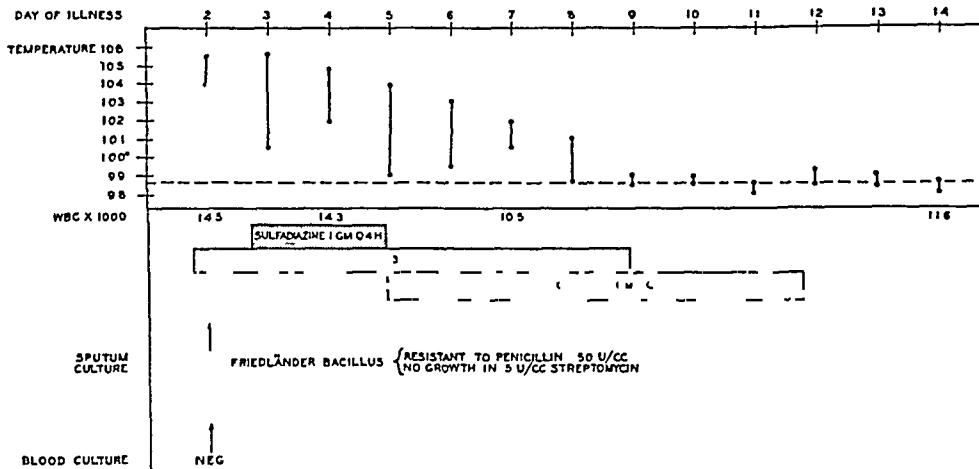


Chart 1 (case 5) —Clinical data recorded for W. M., a soldier 37 years old, who was treated with streptomycin for lobar pneumonia caused by *Klebsiella pneumoniae*.

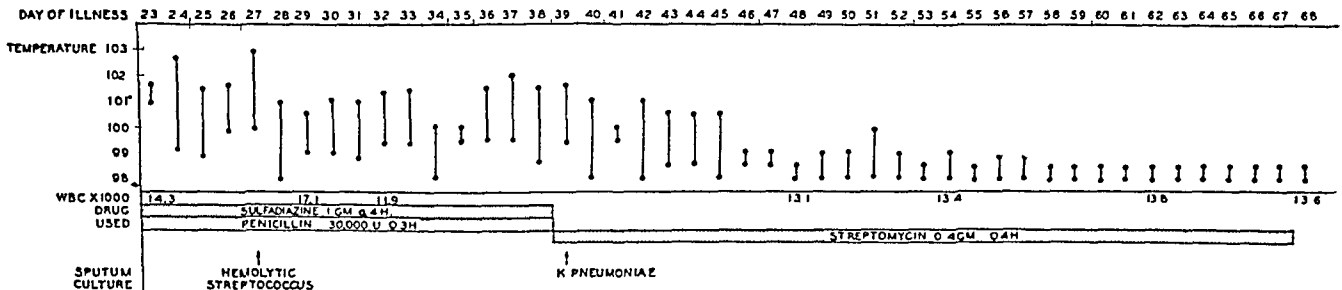


Chart 2 (case 6) —Clinical data recorded for E. M., a veteran 35 years old, who was treated with streptomycin for lobar pneumonia caused by *Klebsiella pneumoniae*.

consolidation over the entire right lung, shown both by physical and by roentgen examination. Culture of sputum then revealed Friedlander's bacilli. Streptomycin was immediately administered, being given in 0.25 Gm doses every three hours together with penicillin. Within twelve hours after this therapy had been started there was a definite decrease in dyspnea and cyanosis as well as an increase in well-being. The patient's temperature subsided within seventy-two hours, and the lung fields gradually cleared.

CASE 6—A 35 year old veteran with a five month history of cough began to have chills and fever approximately three weeks before admission. Examination revealed dullness, diminished resonance and medium loud fine rales over the

upper half of the left side of the chest. Roentgenograms showed evidence of pneumonia involving the upper lobe of the left lung with cavitation. The patient continued to have an intermittent high fever in spite of combined penicillin and sulfadiazine therapy. On the nineteenth day of hospitalization, after a report that *K. pneumoniae* predominated in the sputum, streptomycin therapy was started, 0.4 Gm was given every four hours for sixteen days. The patient's temperature subsided to normal in six days and remained normal. In the ensuing month there was progressive clinical improvement. However, roentgenograms showed persisting consolidation and cavitation in the involved lobe.

In each of the foregoing 6 instances the patient remained critically ill in spite of initial empiric treatment with penicillin, alone or in combination with sulfadiazine. After sputum cultures showed Friedlander bacilli predominating, a change to streptomycin therapy was made. The response was striking in all instances, but complete clearing of the lungs varied according to the duration of the infection. Certainly, on the basis of this small experience streptomycin therapy is indicated in cases of pneumonia due to the Friedlander organisms.

HEMOPHILUS INFLUENZAE PNEUMONIA

CASE 7—An officer aged 26 was admitted to the hospital after being ill for a week with an infection of the upper respiratory tract with chills and fever for one day. Physical examination revealed dulness and rales over the lower lobe of the right lung. His temperature was 103 F. Penicillin therapy was started, 50,000 units being administered every three hours. The dulness increased rapidly, although the temperature subsided somewhat. On the second hospital day bacilli resembling *H. influenzae* were seen in the sputum in great numbers, and were identified as *H. influenzae* subsequently. Streptomycin was substituted for penicillin, 0.4 Gm being given every four hours. The consolidation decreased markedly after three days of this therapy and disappeared after five. By that time the patient was asymptomatic.

CASE 8—In a 23 year old soldier with persistent atypical pneumonia of the right lung there suddenly developed a temperature of 103 F, nausea, vomiting and a pulse rate of 150. Roentgen examination showed pneumonic infiltration of the lower lobe of the left lung. The patient was given 50,000 units of penicillin every three hours and placed in an oxygen tent. After four days of therapy the entire left lung was seen to be involved. The patient was clinically unimproved. Streptomycin therapy was then started, and 0.25 Gm was given every three hours for six days. In forty-eight hours the temperature fell to normal. The lungs were clear in nine days.

The results of the treatment of the 2 patients with pulmonary consolidation in which *H. influenzae* was implicated were fully as gratifying as previous reports had led us to expect.

PULMONARY TULAREMIA (3 CASES)

Three cases of pulmonary consolidation secondary to ulceroglandular tularemia have been reported previously. The patients were all young men, acutely ill, with high temperatures and general malaise, and had been shown to be infected

with *P. tularensis* either by rise of blood serum agglutinins or by the result of a bacteriologic examination of sputum. Streptomycin treatment was started on the seventh, twenty-first and thirty-second days of the disease, respectively, 1 to 2 Gm being given each day. Temperatures subsided to normal within three to seven days, from levels of 104 to 105 F. The lung fields cleared in from two to four weeks.

These results, in general, confirm the published reports of the efficacy of streptomycin therapy in cases of tularemia.

COCCAL PNEUMONIA (2 CASES)

Two patients were critically ill with pneumonia due to infections which proved refractory to treatment with penicillin, though 50,000 units was administered every three hours. The first, an 18 year old white youth, was coughing up large amounts of frothy yellowish sputum containing many hemolytic streptococci. He had dulness, as well as roentgen evidence of consolidation, over the entire right lung and the upper lobe of the left lung. Streptomycin therapy was begun on the eleventh day of the disease, with 0.25 Gm being given every three hours. This therapy resulted in gradual clearing of the chest, decrease in the volume of sputum and falling of the temperature by lysis over a period of five days. The drug was administered for ten days.

The second patient, a 17 year old soldier, had sudden sharp stabbing pain over the right lung and a temperature of 103 F seven days after undergoing appendectomy. There was roentgenologic and clinical evidence of lobar pneumonia. The initial bacteriologic examination of the sputum suggested that *K. pneumoniae* was present. In view of this, streptomycin was administered at the rate of 0.5 Gm every four hours for a total of 3 Gm. His temperature, however, showed no diminution after one and one-half days of therapy. In the meantime, *Pneumococcus* type IX was found in the pretreatment blood culture. Penicillin and sulfadiazine therapy in combination, substituted for streptomycin treatment, effected clearing of the pneumonia in seven days.

In the management of coccal pneumonias trial of streptomycin should be reserved for a final effort, to be made after the use of penicillin or sulfonamide drugs has failed.

PERTUSSIS WITH BRONCHOPNEUMONIA (2 CASES)

A 6 year old boy with typical clinical pertussis and bronchopneumonia but negative cough plates was given 0.25 Gm of streptomycin every three hours for four days. The pneumonia cleared and the cough appeared decreased, but otherwise the course of the disease was not unusual.

A 4 year old girl with bronchopneumonia and pertussis had a similar course after four days of streptomycin therapy. The clinical improvement was not associated with roentgenologic evidence of clearing of the lungs.

Streptomycin may have shortened the course of the disease in these 2 children, but the actual effect of the drug is difficult to evaluate. Additional experience is necessary before any conclusions can be drawn.

OTHER PNEUMONIA (2 CASES)

In a 28 year old woman with a history of thyrotoxicosis unrelieved by two operations, severe agranulocytosis developed after two weeks' treatment with thiouracil. In spite of penicillin therapy, pneumonia developed. Her temperature reached 107 F, and her leukocyte count dropped to 800, with no granulocytes being seen. No predominating organisms were cultured. However, streptomycin was given in addition to the penicillin, and the patient survived the agranulocytic period of seven days.

In a young soldier primary atypical pneumonia developed, following bronchitis. A seven day course of parenteral streptomycin therapy was without effect.

Streptomycin apparently exerted a favorable influence in the first patient, in the second it was without effect.

DISEASES OF THE TRACHEOBRONCHIAL TREE (15 CASES)

Streptomycin was tested therapeutically in 3 cases of asthma accompanying chronic infection of the upper respiratory tract, 6 cases of chronic bronchitis and 6 cases of bronchiectasis.

Asthma with Chronic Infection of the Upper Respiratory Tract—Streptomycin was administered by injection or by introduction of an aerosol or by a combination of the two methods. The susceptible organisms were inconstantly eliminated without clinical improvement in any of the 3 patients.

Bronchitis—Six patients with chronic bronchitis were given streptomycin alone or combined with other therapeutic agents and by both the respiratory and the intramuscular route. The bacteriologic study showed in each case a mixed flora, with gram-negative organisms present in all cases. Gram-negative organisms were eliminated in 4 of the patients, with symptomatic relief in 1. No sustained clinical improvement occurred in 5 patients. The patient in whom clinical improvement was sustained had been treated by a combination of penicillin and streptomycin therapy.

Bronchiectasis—Six patients with bronchiectasis were given streptomycin alone or in combination with penicillin and the streptomycin was administered by intramuscular injection or by introduction by aerosol or by both methods. All the patients had been treated previously with penicillin, administered by intramuscular injection or by introduction of an aerosol, with only slight improvement in their clinical condition. In each instance the organisms were predominantly gram-negative, and therefore streptomycin was believed to be indicated. The usual aerosol dosage was 0.1 Gm four times daily. Two patients receiving streptomycin and penicillin were definitely improved by virtue of the elimination of susceptible bacteria, the reduction of sputum, the gain of weight and the symptomatic relief. In a third patient, receiving streptomycin alone, the sputum changed from mucopurulent to mucoid, although the quantity was not reduced. There was some subjective clinical improvement, but the actual beneficial effects of the streptomycin therapy are doubtful. In the 3 remaining patients the streptomycin had no effect in either the volume or the character of the sputum or on the patients subjectively.

Asthma related to infection of the upper respiratory tract does not seem to be favorably influenced by streptomycin therapy. Bronchitis like-

wise does not seem to be a condition favorable for this therapy, since only 1 patient in 6 showed temporary improvement. In the patients with bronchiectasis the results are equivocal, 2 patients receiving streptomycin and penicillin improved, 1 patient given streptomycin alone possibly improved, and 3 patients receiving only streptomycin were unimproved. It would seem that the best results are obtained when penicillin is given in combination with streptomycin by both the intratracheal and the intramuscular route.

OTHER DISEASES OF THE CHEST CAVITY (12 CASES)

In this category are grouped 3 cases of mycotic infection, 7 cases of pulmonary sarcoidosis and 2 cases of Hodgkin's disease.

Actinomycosis—CASE 9—The patient was a 20 year old man. Two weeks after he had apparently recovered from pneumonia, a fluctuant swelling developed over the left lateral and anterior wall of the chest. It was incised, and *Nocardia asteroides* was isolated. Despite the administration of iodides, sulfonamide compounds and massive doses of penicillin, the disease became widely disseminated, with multiple abscess formation. The fungus, which is aerobic and acid fast, was found to be sensitive to a concentration of streptomycin of 5 micrograms per cubic centimeter and resistant to penicillin. For this reason streptomycin was given, 0.5 Gm. being injected intramuscularly every four hours for twenty-four days. As a result of this treatment, several cultures of material taken from the lesion of the chest showed no growth of the fungus, and there was marked general improvement. However, severe toxic symptoms developed, chiefly nausea, vomiting, vertigo and tinnitus. Streptomycin was withdrawn. The patient again became ill, and the cultures showed growth of the fungus. A second course of streptomycin was given, lasting two weeks. Again the fungus could not be isolated from the lesions, but the general improvement was not as definite as that following the first course of therapy. Once more nausea and vomiting developed. The use of the drug had to be discontinued. A subsequent course of local application of streptomycin was ineffective. Cultures showed that the organism was now resistant to a concentration of streptomycin of 30 micrograms per cubic centimeter. "Pentamidine" (4,4' [pentamethylenedioxy] dibenzamidine) was given for about one week, but the patient died.

In this instance *N. asteroides* was resistant to penicillin but sensitive to streptomycin. After the patient had shown an initial good response to a course of streptomycin therapy, the fungus became resistant, and further administration of the drug was of no avail.

Blastomycosis—CASE 10—A 22 year old white man had chronic disease of the respiratory tract and also involvement of the chest wall. Biopsy of removed material revealed blastomycetes. The disease progressed in spite of trials of various chemotherapeutic agents. Administration of streptomycin was then begun, and 86.4 Gm. was given over a twenty-seven day period. The patient showed progressive improvement, which has been sustained during an eight month follow-up period.

The response in this patient, while not spectacular, was sufficiently gratifying to justify reporting the case at this time in view of the lack of chemotherapeutic agents effective against the disease, the outcome of which is usually fatal.

Moniliasis—A 32 year old man was presumed to have pulmonary tuberculosis, but tubercle bacilli were not observed in his sputum, and ultimately he was found to have pulmonary moniliasis. He was given 1.8 Gm of streptomycin a day intramuscularly in divided doses over a period of forty-two days. During the period of therapy there was a decrease of fever and cough. This improvement was attributed to suppression of secondary invaders, since the monilias were resistant to streptomycin in vitro. Serial roentgenograms showed no alteration during the use of streptomycin. Subsequent intravenous use of methylosaniline chloride U.S.P. (gentian violet) was coincident with apparent cure.

Pulmonary Sarcoidosis—Seven patients with pulmonary sarcoidosis were given streptomycin parenterally in amounts of 1 or 2 Gm daily for periods of thirteen to one hundred and twelve days. No improvement followed in 6 patients. The seventh patient, during bronchoscopic examination, underwent inadvertent perforation of the wall of the esophagus. Mediastinitis resulted, with some consolidation of the base of the right lung and pleural effusion. A two week course of streptomycin therapy, 0.25 Gm being given every four hours, resulted in clearing of the mediastinitis. The fibrosis, however, was as extensive as formerly.

Two patients with advanced mediastinal and abdominal Hodgkin's disease showed no response to streptomycin therapy.

Streptomycin therapy was of no value in the diseases of uncertain or unknown cause encountered in this series.

SUMMARY AND CONCLUSIONS

Six patients with pneumonia due to *Klebsiella pneumoniae* (Friedlander's bacillus) were benefited by courses of streptomycin therapy in which 0.25 to 0.4 Gm was injected intramuscularly every three or four hours for periods of six to sixteen days. The degree of clearing of the lungs was proportionate to the duration of the infection.

Two patients with pneumonia in which *Hemophilus influenzae* (Pfeiffer's bacillus) was implicated responded rapidly to streptomycin.

Streptomycin is indicated for pleuropulmonary tularemia.

Patients with coccal pneumonias should be treated with streptomycin only after trial of other chemotherapeutic agents.

In 2 patients who had pertussis with bronchopneumonia no dramatic alteration of the course of the disease attended streptomycin therapy.

A patient treated with streptomycin and penicillin survived pneumonia with seven days of agranulocytosis.

Streptomycin was of no value in the treatment of 1 patient with atypical pneumonia.

One patient with blastomycosis, 1 with actinomycosis and 1 with moniliasis were treated with streptomycin. Sustained improvement and lasting remission were observed in the patient with blastomycosis. The patient who had actinomycosis showed remission only while under treat-

ment No effect of streptomycin therapy was noted in the patient with moniliasis

Streptomycin was of no value in the treatment of patients with chronic bronchitis

Asthma accompanying chronic infection of the upper respiratory tract and Hodgkin's disease, pulmonary sarcoidosis and other conditions of unknown cause are not influenced by streptomycin

ADDENDUM

Since completion of this paper 6 additional cases in which the patient was treated with streptomycin have been fully studied They are as follows

KLEBSIELLA PNEUMONIAE PNEUMONIA (1 CASE)

The lower lobes of the right and left lungs were involved Streptomycin was administered for ten days after no effect was obtained with combined penicillin and sulfadiazine therapy Twenty-four hours after the first dose of streptomycin was given, the temperature fell from 105 F to normal levels, and there was marked clinical improvement, which was sustained and progressive

HEMOPHILUS INFLUENZAE PNEUMONIA (1 CASE)

The lower lobes of the right and left lungs were involved The patient, a 15 year old youth, showed marked clinical improvement within seventy-two hours after the onset of streptomycin therapy (0.25 Gm every three hours) and steady improvement thereafter Thirty grams of streptomycin were given over a fifteen day period

VIRUS PNEUMONIA WITH SECONDARY PSEUDOMONAS AERUGINOSA INFECTION (1 CASE)

A 57 year old man with atypical pneumonia involving the lower lobe of the left lung suddenly became worse after twelve days of penicillin therapy The sputum changed from blood tinged to mucopurulent Cultures showed *Ps. aeruginosa* predominating, sensitive to streptomycin He was then treated with this antibiotic, 1 Gm being injected intramuscularly three times daily for eight days The patient showed a slow, satisfactory response with an immediate encouraging decrease of sputum The organisms, however, were not eliminated from the sputum and became drug fast The patient became afebrile and symptom free on the eighth day of streptomycin therapy and remained so

CHRONIC BRONCHITIS WITH CYLINDRIC BRONCHIECTASIS OF THE LOWER LOBE (2 CASES)

No benefit followed a two week course of combined treatment—acerosol (0.1 Gm four times daily) and parenteral streptomycin (0.25 Gm six times daily)

SILICOSIS (1 CASE)

A 46 year old man who had complained of cough and expectoration for six months revealed on roentgen examination splotchy, patchy infiltration throughout all lobes of both lungs, which appeared to include a moderate element of fibrosis. After one month of resting in bed there was no improvement. Streptomycin was given in a dose of 2 Gm daily for eighty days. The condition of the patient deteriorated rapidly, and he died. At autopsy there was no gross evidence of tuberculosis. The findings were consistent with a diagnosis of severe silicosis.

BACTERIOLOGIC AND IMMUNOLOGIC STUDIES ON PATIENTS WITH HEMOLYTIC STREPTOCOCCIC INFECTIONS AS RELATED TO RHEUMATIC FEVER

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NUMEROUS investigators have studied the antibody responses of patients with either complicated or uncomplicated streptococcic infections, but only a few workers¹ have dealt with more than one or two of the antibodies to the known antigenic components of group A hemolytic streptococci. Moreover, reports which have dealt with the antibody response of patients with streptococcic complications and sequelae rarely included the period of the acute streptococcic infection in the study.

Antistreptolysin O and antifibrinolysin have been the two antibodies most commonly studied. Todd² originally showed that the serum antistreptolysin O titer was increased after hemolytic streptococcic infections and during the active stage of rheumatic fever. Tillett, Edwards and

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1 (a) McEwen, C., Bunim, J. J., and Alexander, R. C. Bacteriologic and Immunologic Studies in Arthritis. II Results of Various Immunologic Tests in Different Forms of Arthritis, *J Lab & Clin Med* **21** 465, 1936. (b) Spink, W. W., and Keefer, C. S. Studies of Hemolytic Streptococcal Infections. II The Serological Reactions of the Blood During Erysipelas, *J Clin Investigation* **15** 21, 1936. (c) Mote, J. R., and Jones, T. D. Studies of Hemolytic Streptococcal Antibodies in Control Groups, Rheumatic Fever, and Rheumatoid Arthritis. II The Frequency of Antistreptolysin "O," Antifibrinolysin, and Precipitating-Antibody Responses in Scarlet Fever, Hemolytic Streptococcal Infections, and Rheumatic Fever, *J Immunol* **41** 61, 1941. III The Magnitude of Anti-Streptolysin "O," Antifibrinolysin, and Precipitating-Antibody Responses, the Persistence of the Antibodies and Variations in Antistreptolysin "O" Curves in Scarlet Fever, Hemolytic Streptococcal Infections and Rheumatic Fever, *ibid* **41** 87, 1941.

2 Todd, E. W. Antihaemolysin Titres in Haemolytic Streptococcal Infections and Their Significance in Rheumatic Fever, *Brit J Exper Path* **13** 248, 1932.

Garner³ were the first to show that the plasma clot of most patients convalescent from acute hemolytic streptococcal infections became resistant to lysis by a standard culture of hemolytic streptococci, and Hadfield, Magee and Perry⁴ observed that the plasma clots from patients with rheumatic fever were also resistant to lysis in the great majority of cases. These observations have been confirmed by many other workers. Antibodies in convalescent human serums against several other antigens of group A streptococci have also been studied, namely antistreptolysin S,⁵ type-specific anti-M precipitins,⁶ group A specific anti-C carbohydrate precipitins^{1a} and bactericidal and bacteriostatic antibodies.⁷ Type-specific agglutinins for homologous streptococci were also observed,⁸ and mouse-protective antibodies were demonstrated in serums of patients recovering from group A streptococcal infections.⁹

Not only have many of these serologic studies revealed a close relationship between hemolytic streptococcal infections and rheumatic fever but they have also been applied by certain investigators to show possible differences in the antibody response between streptococci-infected patients in whom rheumatic fever developed and those in whom it did

3 Tillett, W. S., Edwards, L. B., and Garner, R. L. Fibrinolytic Activity of Hemolytic Streptococci. The Development of Resistance to Fibrinolysis Following Acute Hemolytic Streptococcus Infections, *J. Clin. Investigation* **13** 47, 1934.

4 Hadfield, G., Magee, V., and Perry, C. B. The Lysis of Fibrin by Streptococci. Its Application to the Problems of Rheumatic Infection in Children, *Lancet* **1** 834, 1934.

5 Todd E. W., Coburn, A. F., and Hill, A. B. Antistreptolysin S Titres in Rheumatic Fever, *Lancet* **2** 1213, 1939.

6 (a) Swift, H. F., and Hodge, B. E. Type Specific Anti-M Precipitins in Rheumatic and Non-Rheumatic Patients with Hemolytic Streptococcal Infections, *Proc. Soc. Exper. Biol. & Med.* **34** 849, 1936. (b) Coburn, A. F. Observations on the Mechanism of Rheumatic Fever, *Lancet* **2** 1025, 1936.

7 (a) Todd E. W. The Influence of Sera Obtained from Cases of Streptococcal Septicaemia on the Virulence of the Homologous Cocci, *Brit. J. Exper. Path.* **8** 361, 1927. (b) Hare, R. Alterations in the Bactericidal Power of the Blood Which Occur During Haemolytic Streptococcal Infections in the Puerperium, *J. Path. & Bact.* **41** 61, 1935. (c) Kuttner, A. G. and Lenert, T. F. The Occurrence of Bacteriostatic Properties in the Blood of Patients After Recovery from Streptococcal Pharyngitis, *J. Clin. Investigation* **23** 151, 1944. (d) Rothbard, S. Bacteriostatic Effect of Human Sera on Group A Streptococci. I. Type-Specific Antibodies in Sera of Patients Convalescent from Group A Streptococcal Pharyngitis, *J. Exper. Med.* **82** 93, 1945. Spink and Keefer^{1b}

8 Walker, D. W. Application of the Technique of Slide Agglutination of Hemolytic Streptococci to Human Sera, *Proc. Soc. Exper. Biol. & Med.* **48** 338, 1941. Rantz, L. A., Kirby, W. M. M., and Jacobs, A. H. Group A Hemolytic Streptococcus Antibodies. Griffith Type Agglutinin and Antistreptolysin Titers in Normal Men and in Acute Infections, *J. Clin. Investigation* **22** 411, 1943.

9 Diefendorf, H. W. A Method for Detecting in Human Serum Protective Bodies Against Hemolytic Streptococci, *Proc. Soc. Exper. Biol. & Med.* **48** 56, 1941.

not For instance, Todd, Coburn and Hill⁵ observed a contrast between the low (but increased above the normal) antistreptolysin S titer and the high antistreptolysin O titer in the serums of patients with active rheumatic fever, whereas both antistreptolysin O and antistreptolysin S titers were definitely increased in the absence of rheumatic activity after streptococcic infections Swift and Hodge^{6a} observed that anti-M precipitins appeared later in patients in whom rheumatic fever developed than in those in whom this sequela failed to appear Coburn^{6b} found that the antibody responses to streptolysin O and the type-specific M protein were delayed in rheumatic patients in whom recurrent attacks of rheumatic fever developed as compared with those who escaped recurrences after hemolytic streptococcic pharyngitis Kuttner and Krumwiede,¹⁰ on the other hand, have not been able to find a delayed antibody response to streptolysin O in patients in whom rheumatic fever developed after hemolytic streptococcic infections

It is now generally believed that rheumatic fever is usually, if not invariably, preceded by infections with group A hemolytic streptococci The mechanism by which the streptococcic infection activates rheumatic fever is still unknown If by means of antibody studies it could be shown that rheumatic fever following streptococcic infections is characterized by a different antibody pattern than that which occurs in comparable subjects in whom rheumatic fever does not develop, then further insight might be gained concerning the mechanism by which streptococcic infections activate this disease It appeared advisable, therefore, to extend this type of investigation for the following reasons Many previous immunologic studies began with the period of rheumatic fever and neglected the acute streptococcic phase Most previous investigators employed only one or two antibody reactions to hemolytic streptococcic antigens There is still disagreement as to whether the antibody response of the rheumatic patient differs appreciably from that of the non-rheumatic patient

All patients were followed from the time of onset of the acute streptococcic infection through the period of complications and sequelae until convalescence was well established Serums obtained at weekly intervals were tested for the following responses

1 Reactions induced by group A streptococci without regard to type, which included (a) antistreptolysin O, (b) antifibrinolysin, (c) precipitins against group A specific carbohydrate C and (d) precipitins against a nucleoprotein fraction obtained from group A streptococci

10 Kuttner, A G, and Krumwiede, E Observations on the Effect of Streptococcal Upper Respiratory Infections on Rheumatic Children A Three Year Study, *J Clin Investigation* 20 273, 1941

2 Reactions to type-specific components of group A streptococci, which included (a) type-specific anti-M precipitins and (b) type-specific bacteriostatic antibodies

3 Reactions having no demonstrable specific relationship to streptococcal infections, which included (a) precipitins against pneumococcal "C" polysaccharide and (b) phase precipitin reactions (in 9 patients in whom rheumatic fever developed)

MATERIALS AND METHODS

Clinical Study—From October 1940 to June 1944 a series of rheumatic and nonrheumatic subjects suffering from definite group A streptococcal nasopharyngitis was observed. They were invariably hospitalized early in the course of the primary streptococcal disease. To prevent cross infections with other types of streptococci, each patient was isolated until two successive cultures of the throat and nasopharynx, taken at least twenty-four hours apart, revealed no hemolytic streptococci. On their admission to the hospital, a complete history was recorded and a physical examination made, daily changes in signs and symptoms were uniformly documented. Routine total erythrocyte, leukocyte and differential counts, estimations of hemoglobin content, and erythrocyte sedimentation rate (Westergren), cultures of material from the nasopharynx and throat, examination of urine, electrocardiographic studies, and roentgenologic studies of the heart and lungs and the paranasal sinuses when indicated, were done at the time of entry to the hospital. Blood samples for serologic studies were obtained on admission, and at weekly intervals thereafter. In addition, serial weekly total leukocyte counts, examination of urine, electrocardiographic studies, determinations of erythrocyte sedimentation rates and cultures of material from the nasopharynx and throat (until two successive cultures taken twenty-four hours apart were sterile for hemolytic streptococci) were done.

Only symptomatic therapy was employed during the acute streptococcal phase of the illness, but patients with purulent complications were treated with sulfadiazine, many of them were also given therapeutic doses of sulfadiazine in an effort to clear up the streptococcal carrier state. All patients with rheumatic fever received adequate doses of salicylates to eliminate symptoms and fever, and this was continued throughout the period of rheumatic activity. For 1 patient it was necessary to use "pyramidon" (aminopyrine).

After discharge from the hospital, many of the rheumatic subjects were examined in the outpatient department at intervals of three to four weeks, if subsequent infections occurred, they were immediately readmitted for study.

Bacteriologic Methods—Cultures of the nasopharynxes were obtained by passing a sterile swab through each nostril to the posterior pharyngeal wall, throat cultures were made by swabbing both tonsils or tonsillar fossae and the posterior pharynx. The swabs were streaked immediately in duplicate on fresh 5 per cent rabbit and sheep blood agar plates. Typical representative colonies were then picked and streaked on other blood agar plates for further identification or transferred directly to broth for classification. The hemolytic streptococci were grouped and typed by the precipitin technic¹¹

11 Lancefield, R. C. The Antigenic Complex of *Streptococcus Haemolyticus* I. Demonstration of a Type-Specific Substance in Extracts of *Streptococcus Haemolyticus*, J. Exper. Med. 47: 91, 1928. Swift, H. F., Wilson, A. T., and Lancefield, R. C. Typing Group A Hemolytic Streptococci by M Precipitin Reactions in Capillary Pipettes, J. Exper. Med. 78: 127, 1943.

Serologic Technics—Determinations of antistreptolysin O titers were made according to Todd's method¹² modified as previously described¹³. The anti-fibrinolysin tests were performed by the method of Tillett, Edwards and Garner³ and that of Boisvert¹⁴.

For the various precipitin tests, the following reagents were employed. The group A specific carbohydrate C was made by Fuller's formamide method¹⁵ and used in the dilution which gave maximal precipitation with hyperimmune rabbit serum. The type-specific M extracts, prepared according to Lancefield's technic,¹⁶ were tested for type specificity with absorbed immune rabbit serum of homologous and heterologous types and were proved free of group-specific C substance by the employment of suitable antisera. The streptococcic nucleoprotein fraction¹⁸ was used in a concentration of 5 mg of dry weight per cubic centimeter of diluent. The C-reactive protein was determined according to the method of Tillett and Francis¹⁷ with a pneumococcus C polysaccharide¹⁸ in a concentration of 10 mg per hundred cubic centimeters. The phase precipitin test¹⁹ was performed according to the method of Coburn and Pauli.²⁰

The reaction to the bacteriostatic test, previously described,^{7d} was considered positive only if there was at least a 2 plus difference in growth from at least two different dilutions as compared with the corresponding streptococcus dilution control.²¹

OBSERVATIONS AND RESULTS

Clinical and Bacteriologic Observations—A total of 153 patients were studied, 128 males and 25 females. Their ages ranged between 3 and 45 years, 19 patients were in the first decade, 54 in the second,

12 Todd, E. W. Antigenic Streptococcal Hemolysin, *J. Exper. Med.* **55**: 267, 1932.

13 Hodge, B. E., and Swift, H. F. Varying Hemolytic and Constant Combining Capacity of Streptolysins. Influence on Testing for Antistreptolysins, *J. Exper. Med.* **58**: 277, 1933.

14 Boisvert, P. J. The Streptococcal Antifibrinolysin Test in Clinical Use, *J. Clin. Investigation* **19**: 65, 1940.

15 Fuller, A. T. The Formamide Method for Extraction of Polysaccharides from Haemolytic Streptococci, *Brit. J. Exper. Path.* **19**: 130, 1938.

16 Lancefield, R. C. The Immunological Relationships of Streptococcus Viridans and Certain of Its Chemical Fractions. I. Serological Reactions Obtained with Antibacterial Sera, *J. Exper. Med.* **42**: 377, 1925.

17 Tillett, W. S., and Francis, T., Jr. Serological Reactions in Pneumonia with a Non-Protein Somatic Fraction of Pneumococcus, *J. Exper. Med.* **52**: 561, 1930.

18 With pneumococcus C polysaccharide extract 0.15 cc of antigen was mixed with an equal volume of undiluted test serum.

19 For the phase precipitin test, 0.1 cc of antibody serum (phase III serum in acute stage of rheumatic fever) was layered over 0.1 cc of antigen serum (phase II, prerheumatic or poststreptococcal stage).

20 Coburn, A. F., and Pauli, R. H. A Precipitinogen in the Serum Prior to the Onset of Acute Rheumatism, *J. Exper. Med.* **69**: 143, 1939.

21 The blood was obtained from children with noninfectious orthopedic disturbances in the New York Orthopedic Hospital, the Hospital for Special Surgery and the New York Hospital through the assistance of Dr. Philip D. Wilson, Dr. Alan De Forest Smith and Dr. S. Z. Levine.

62 in the third, 14 in the fourth and 4 in the fifth. The 153 patients suffered a total of 169 definite hemolytic streptococcic infections of the upper respiratory tract, and in every instance relatively large numbers of hemolytic streptococci, often in almost pure culture, were recovered from the patients' nasopharynxes. Fifty-four different infections were experienced by a group of 39 patients known to have had one or more attacks of rheumatic fever previously, 115 infections occurred among 114 nonrheumatic subjects. In several cases definite clinical evidence of infection was not present, although large numbers of hemolytic streptococci appeared in nose and throat cultures of patients who shortly before had not harbored these micro-organisms and who later had a definite increase of antistreptolysin O. Among the 39 known rheumatic subjects who suffered 54 hemolytic streptococcic infections, there were 17 recurrences of rheumatic fever. Three of these patients each had two separate attacks of rheumatic fever after infections with different types of group A streptococci. Rheumatic fever developed in 21 of the 114 previously nonrheumatic subjects who experienced 115 streptococcic infections. The patients with rheumatic fever had polyarthritides and carditis and at the same time increased leukocyte counts and erythrocyte sedimentation rates, a few patients,²² however, with accompanying secondary rises in blood leukocyte counts and/or sedimentation rates had only carditis after their streptococcic infections.

Scarlet fever characterized 114 of the 169 infections, but in the following analysis the group with this disease are not differentiated from patients with tonsillitis or pharyngitis without a rash, since many of the patients who in the same epidemic failed to show a rash were infected with the same type of streptococcus as those in whom a scarlatiniform rash developed.

The data given in table 1 show the distribution of the serologic groups and types of streptococci cultured in material from the 153 patients during their 169 attacks of acute pharyngitis, 102 of the attacks were uncomplicated, 29 resulted in purulent complications during the first to the fourth week (average 1.6 weeks) due to the same streptococcic type which caused the initial infection and 38 were followed by acute rheumatic fever. In 4 of these 38 there were also purulent complications. Rheumatic sequelae occurred during the first to the eighth week (average 3.4 weeks) after the onset of the streptococcic infection.

Six of the streptococcic strains belonged to group C, one to group G and one hundred and sixty-two to group A. Twenty-two or 13.6 per cent, of the group A strains failed to type by the anti-M precipitin method with diagnostic serums representing thirty-seven different serologic

²² Watson, R. F., Rothbard, S., and Swift, H. F. The Relationship of Postscarlatinal Arthritis and Carditis to Rheumatic Fever, *J. A. M. A.* **128**: 1145 (Aug. 18) 1945.

types, although three of these were proved to contain the T antigen of type 14 by the agglutination technic. In 5 instances two types were recovered, the type listed first in table 1 was considered probably responsible for the infection. Type 19 predominated in all three clinical groups and made up 45.3 per cent of the infecting strains of group A streptococci. The preponderance of this type among the patients was due to the inclusion of naval personnel involved in an epidemic of scarlet fever.

TABLE 1—*Serologic Classification of Streptococci Isolated from Patients with Acute Pharyngitis Correlated with the Development of Complications**

		No. of Streptococcic Infections Associated with			Total
		No Complications	Purulent Complications	Rheumatic Fever	
Group A	Type				
	1	3	1	1	5
	3	9	1	1	11
	3-14†	1			1
	5	1			1
	6	5	2	2	9
	6-14†	1	1		2
	12	2			2
	14	3		2	5
	17	3	2	2	7
	18	2			2
	19	38	13	17	68
	19-6†	1	1	1	3
	23	1	1		2
	26	2	1	3	6
	29	1			1
	30	6	2		8
	32			1	1
	33	1		1	2
	38	3			3
	39	1			1
	45	1			1
	NC‡	11	4	7	22
Group C		6			6
Group G		1			1
Totals		102	29	38	169

*A total of 153 patients suffered 169 different streptococcic infections.

†Streptococci of two types were recovered from these patients. The type listed first was considered probably responsible for the infection.

‡These strains could not be classified into types by the precipitin technic, but one in the group with no complications and two in the group with purulent complications were proved by the agglutination method to contain the T antigen of type 14.

previously reported.²³ It is of interest to note, however, that nine other serologic types, as well as seven unclassified strains, caused infections that were followed by rheumatic fever.

It is also of interest that the 7 hemolytic streptococcic infections not of group A were not followed by rheumatic fever although 5 of them occurred in patients who were known to have had rheumatic fever previously and who were therefore presumably susceptible to the disease.

23 Watson, R. F., Schwentker, F. F., Fetherston, J. E., and Rothbard, S. Sulfadiazine Prophylaxis in an Epidemic of Scarlet Fever, *J. A. M. A.* **122**: 730 (July 10) 1943.

In fact, in 1 of these rheumatic subjects a recurrent attack of rheumatic fever subsequently developed after a group A streptococcal infection. It is significant that no single serologic type of group A streptococci could be correlated with the development of either purulent complications or rheumatic fever. The distribution of the various serologic types was approximately the same in patients who made uneventful recoveries as in those in whom complications or sequelae developed.

Antibody Studies—A summary of the results of the antistreptolysin O titrations and the antifibrinolysin determinations made on the serums and plasma respectively of the patients without complications and of those who suffered purulent complications or rheumatic fever after

TABLE 2—Summary of Weekly Determinations of Antistreptolysin O and Antifibrinolysin Correlated with the Type of Clinical Reaction to Streptococcal Infections

Complications and Sequelae		None	Purulent	Rheumatic Fever	Total
ANTISTREPTOLYSIN O					
Number of infections		102	29	38	169
Increased titers	Number	78	22	32	132
	Per cent	76.4	75.9	84.2	78.1
Beginning of rise*	Weeks	2.1	2.2	2.0	2.2
Maximal level*	Weeks	4.7	3.0	5.5	4.8
Maximal level (units/cc)†					
Initial level (units/cc)	Ratio	3.8	9.3	5.1	5.0
ANTIFIBRINOLYSIN					
Number of infections		85	26	24	135†
Increased titers	Number	46	17	19	82
	Per cent	54.1	65.4	79.2	60.1
Beginning of rise*	Weeks	2.5	2.7	2.4	2.5
Maximal level*	Weeks	3.4	3.2	3.0	3.2

*Based on average time in weeks after onset of infection.

†An expression of the magnitude of the response, based on the average of the ratios $\frac{\text{maximal level}}{\text{initial level}}$ calculated for each individual patient.

‡In an additional 34 infections (20 per cent) antifibrinolysin determinations could not be made because of high or maximal resistance of the plasma clot to fibrinolysis at the onset of infection.

streptococcal pharyngitis is presented in table 2. The data cover all the determinations made at the time of the acute streptococcal infection and weekly thereafter until the patients were discharged from the hospital. In some instances, further determinations were made from blood samples obtained on subsequent visits to the clinic at three to four week intervals.

A significant increase in the serum antistreptolysin O titer was considered to have occurred only if it increased by two or more dilutions over that shown at the time of the initial determination. In accordance with this criterion, the serum antistreptolysin O titer increased in 76.4 per cent of the patients with uncomplicated pharyngitis, in 75.9 per cent of those in whom purulent complications developed and in 84.2 per cent of those in whom rheumatic fever developed (table 2). The

interval between the onset of infection and the beginning of the rise in the antistreptolysin O titer was essentially the same for the three groups, namely, 21, 22 and 20 weeks respectively. The average interval between the onset of infection and the time at which the maximal titer was reached was 47 weeks for the patients with no complications, 39 weeks for the patients in whom purulent complications developed and 55 weeks for those in whom rheumatic fever developed. In table 2 the magnitude of the serum antistreptolysin O response is expressed as the ratio between the maximal and the initial titers. When the responses of these three groups of patients are compared on this basis, it is evident that the average rise was 9.3 times for the group of patients in whom purulent complications developed, 5.1 times for those in whom rheumatic fever developed and only 3.8 times for those who had no complications. The data seem to indicate that, on the average, patients in whom rheumatic fever develops are more likely to have significant serum antistreptolysin O responses, with slightly delayed maximal titer, and are also likely to have a more intense response than the patients with uncomplicated disease but a less intense response than those who suffer purulent complications. These results, however, are of doubtful significance since the groups studied are small. Moreover, when the individual patients are considered, it is found that there is great variation and considerable overlapping among the members of the three groups.

A total of 132 (78 per cent) of the 169 streptococcic infections resulted in significant rises in the antistreptolysin O titer. The average time for the beginning of the rise in titer was 22 weeks, for the maximal level to be reached, 48 weeks were required. The average maximal-initial ratio was 5.0 times.

The antifibrinolysin was considered significantly increased only if between admission and discharge there was an increase of 2 plus in the results. These tests were less satisfactory for comparison than were the determinations of antistreptolysin O because this test, as employed here, was not quantitative²⁴ and in many instances increase in antifibrinolysin could not be measured because the initial level was too high. Even though the numbers are small, it is noteworthy (table 2) that 79.2 per cent of the patients in whom rheumatic fever developed showed a significant increase in their antifibrinolysin titers whereas only 54.1 per cent of the group without complications and only 65.4 per cent of the patients in whom purulent complications developed showed increased titers. The average time of onset of the initial increase in resistance to lysis of the plasma clot and the time when the maximal level was reached were essentially the same for each group.

²⁴ Since these tests were made, Kaplan has recently devised a quantitative serologic method for the estimation of serum antifibrinolysin which possesses a number of advantages over the plasma test (Kaplan, M. H. *J. Clin. Investigation* 25: 347, 1946).

In a total of 83 (60 per cent) of 135 infections significant increases in the antifibrinolysin titers were observed. The beginning of the rise of antifibrinolysin and the maximal level occurred in 2.5 and 3.2 weeks respectively. Unfortunately, it was not possible to determine the duration of the increase of either antistreptolysin O or antifibrinolysin because many patients were discharged from the hospital before the antibody responses returned to the initial level.

Additional Antibody Studies—From the entire group of 153 patients 71 who suffered 83 different group A streptococcal infections were selected for a more comprehensive study of their antibody responses. These patients were divided into three groups, on the basis of their clinical response to the streptococcal infections, in the same manner in which the large group was considered, namely, (1) those in whom complications failed to develop, (2) those in whom purulent complications developed and (3) those in whom rheumatic fever developed. In addition to determinations of antistreptolysin O and antifibrinolysin, the serums of these patients were tested at weekly intervals for the presence of streptococcal bacteriostatic antibodies and precipitins directed toward the type-specific M protein, the group-specific C carbohydrate and a nucleoprotein fraction of group A streptococci and for the presence of C-reactive protein (against pneumococcus C).

In table 3 are summarized the findings with respect to four different streptococcal antibodies which developed in these 71 patients. The results of the antistreptolysin O titrations for these three groups are essentially the same as those found for the three larger groups and recorded in table 2. The percentage of patients who showed increased antifibrinolysin titers is somewhat higher than that in the larger group. This slight difference is probably due to the difference in the number of cases summarized in the two tables. Because larger groups tend to be more representative, we believe that the figures given in table 2 reflect more accurately the comparative differences between the three groups of patients than those in table 3.

The bacteriostatic and anti-M precipitin tests were employed to determine the presence of type-specific antibodies in the serums of these patients, the results are recorded in table 3. Eighty-eight per cent of the patients in whom rheumatic fever developed had demonstrable type-specific bacteriostatic antibodies, whereas 69 per cent of those with purulent complications and 67 per cent of those without any complications had them. In general, in the patients in whom rheumatic fever developed there was also a slight delay in the appearance of the bacteriostatic antibodies as compared with the two other groups of patients. The individual values, however, spread widely about the average, and some patients (table 3) in whom rheumatic fever developed showed a

bacteriostatic antibody response as early as did those in whom rheumatic fever failed to develop after their streptococcic infection. In general the period for which these antibodies lasted could not be determined because they were still present when the patients left the hospital. In most instances, however, they persisted for at least many months and in some for over two years.

TABLE 3—Summary of Weekly Determinations of Different Streptococcic Antibodies Correlated with the Type of Clinical Reaction to Streptococcic Infections

Complications and Sequelae		None	Purulent	Rheumatic Fever*	Total
ANTISTREPTOLYSIN O					
Number of infections		33	16	34	83
Increased titers	Number	23	12	29	64
	Per cent	69.7	75.0	85.3	77.1
Beginning of rise†	Weeks	2.4	2.3	2.0	2.4
Maximal level†	Weeks	4.2	3.8	5.8	5.3
Maximal level (units/cc)‡	Ratio	4.2	10.6	5.4	6.0
Initial level (units/cc)					
ANTIFIBRINOLYSIS					
Number of infections		27	15	21	63**
†Increased titers	Number	17	12	17	46
	Per cent	62.9	80.0	80.9	73.0
Beginning of rise†	Weeks	3.1	2.5	2.3	2.6
Maximal level†	Weeks	4.2	3.2	3.0	3.5
BACTERIOSTATIC ANTIBODIES					
Number of infections		33	16	33	82
Increased titers	Number	22	11	29	62
	Per cent	66.7	68.8	87.9	75.6
Beginning of rise†	Weeks	4.2	3.9	6.1	5.1
Range†	Weeks	2 to 10	2 to 8	1 to 13	
ANTI-M PRECIPITINS					
Number of infections		33	16	34	83
Increased titers with					
(1) Homologous M antigen	Number	15	9	29	53
	Per cent	45.5	56.2	85.3	63.9
(2) Heterologous M antigens†	Number	10	7	22	39
	Per cent	33.3	43.8	61.8	46.9
Beginning of rise†	Weeks	3.6	2.6	6.0	4.8
Range†	Weeks	1 to 8	1 to 5	1 to 23	

*Four of these patients also had purulent complications.

†Based on average time in weeks after onset of infection.

‡An expression of the magnitude of the response, based on the average of the ratios $\frac{\text{maximal level}}{\text{initial level}}$ calculated for each individual patient.

**In an additional 20 infections, determinations of antifibrinolysin could not be made because of high or maximal resistance of the plasma clot to fibrinolysis at onset of infection.

†Reactions were usually observed with heterologous M antigens in serums which also gave reactions with homologous M antigens.

Although the results of the bacteriostatic test were strikingly type specific, the precipitin reactions with homologous and heterologous M extracts showed little evidence of type specificity. The highest incidence (85.3 per cent) of positive reactions, however, was again found in patients in whom rheumatic fever developed, and the average time of appearance of these antibodies was delayed as compared with that in the other two groups. However, as shown in table 3, cross reactions with

heterologous M extracts were so frequent that little reliance can be placed on the type specificity of the test. Among the patients tested, with a total of 83 infections, 53 showed reactions with homologous M extracts, but 39 of the 53, or 73.6 per cent, showed equally strong reactions with extracts of heterologous types. Furthermore, the serums which reacted with heterologous type extracts usually reacted as well with the homologous type extracts. The results probably can be interpreted best as evidence of response to non-type-specific streptococcic products.

The group-specific carbohydrate C antibody was found in only 5 of the 83 infections, four of the positive reactions occurred with serums of patients in whom attacks of rheumatic fever developed and one with the serum of a patient in whom a suppurative complication developed. The precipitin directed against the nucleoprotein fraction was detected in only 3 patients, in all of whom rheumatic fever developed. In these 3, antibodies against both group-specific C carbohydrate and the nucleoprotein fraction were observed.

The C-Reactive Protein—This protein, contained in the α_1 globulin fraction,²⁵ is precipitated with dilute solutions of pneumococcus "C" polysaccharide and is found in the serum during the acute phase of various infectious diseases.²⁶ Although C-reactive protein is apparently in no way related to the formation of antibodies, it seemed of interest to compare its occurrence and duration in the presence of complications and sequelae following group A streptococcic infections in rheumatic and nonrheumatic subjects.

The results shown in table 4 indicate that the C-reactive protein was observed in 63, or 75.9 per cent, of the 83 infections. In patients showing positive reactions, it was usually detected in the serums obtained during the acute streptococcic phase and during the time of purulent complication as well as in the period of greatest rheumatic activity. It occurred in 51.4 per cent of the patients without complications, in 75 per cent of those with purulent complications and in 97.6 per cent of those in whom rheumatic fever developed.²⁷ The presence of the C-reactive protein in

25 Perlman, E., Bullowa, J. G. M., and Goodkind, R. An Immunological and Electrophoretic Comparison of the Antibody to C Polysaccharide and the C Reactive Protein of Acute Phase Serum, *J. Exper. Med.* **77** 97, 1943.

26 Ash, R. Non-Specific Precipitins for Pneumococcic Fraction C in Acute Infections, *J. Infect. Dis.* **53** 89, 1933. Abernethy, T. J., and Avery, O. T. The Occurrence During Acute Infections of a Protein Not Normally Present in the Blood. I. Distribution of the Reactive Protein in Patients' Sera and the Effect of Calcium on the Flocculation Reaction with C Polysaccharide of the Pneumococcus, *J. Exper. Med.* **73** 173, 1941. Tillett and Francis.²⁷

27 These percentages would probably have been increased if antiserum prepared in rabbits to C-reactive protein from human sources (Macleod, C. M., and Avery, O. T. *J. Exper. Med.* **73** 191, 1941) had been used instead of the "C" polysaccharide.

the serums showed a close correlation with the intensity and duration of the inflammatory reaction of the host, as indicated by the elevated temperatures and increased serial erythrocyte sedimentation rates illustrated in charts 1, 2, 3 and 4. This protein persisted longest in the serums of patients with rheumatic fever.

Phase Precipitins—Escherich and Schick,²⁸ Schlesinger²⁹ and Coburn and Pauli³⁰ described three different clinical phases in the development of rheumatic fever. Phase I represents the acute streptococcic infection, phase II an afebrile and often asymptomatic period and phase III the state of rheumatic fever. A precipitation reaction which sometimes occurs when serums taken in phase II and phase III are mixed has been described by Coburn and Pauli.²⁰ The serum in phase II was considered by them to contain an antigen and that taken in phase III

TABLE 4—Summary of Weekly Determinations of the C-Reactive Protein in Patients with Different Types of Clinical Reactions to Streptococcic Infections

Complications and Sequelae		None	Purulent	Rheumatic Fever	Total
Number of infections		33	16	34	83
Positive reactions	Number	18	12	33	63
	Per cent	51.4	75.0	97.6	75.9

an antibody. These authors recorded no precipitate obtained by mixing phase I and phase II serums or phase I and III serums.

Wedum and Wedum³¹ observed phase precipitin reactions not only with serums from patients with rheumatic fever but also with those from patients with atypical pneumonia and nasopharyngitis, and occasionally with those from apparently normal blood donors.

In the present study, serums which were obtained from 9 patients in all three phases in the evolution of their attacks of rheumatic fever were tested for phase precipitins. In certain cases faint rings were observed at the interface of the two serums, but this occurred as often between the serums obtained in phases I and II or phases I and III as it did between phase II and phase III serums. In other cases no rings or precipitates were observed. It is not clear whether these faint rings represented true precipitin reactions.

²⁸ Escherich, T., and Schick, B., Scharlach, Vienna, A. Holder, 1912.

²⁹ Schlesinger, B. The Relationship of Throat Infection to Acute Rheumatism in Childhood, *Arch. Dis. Childhood* **5**:411, 1930.

³⁰ Coburn, A. F., and Pauli, R. H. Studies on the Relationship of Streptococcus Hemolyticus to the Rheumatic Process. III. Observations on the Immunological Responses of Rheumatic Subjects to Hemolytic Streptococcus, *J. Exper. Med.* **56**:651, 1932.

³¹ Wedum, A. G., and Wedum, B. G. Serum Precipitation Reaction in Rheumatic Fever and in Other Conditions, *Proc. Soc. Exper. Biol. & Med.* **61**:432, 1946.

Details of Findings in Typical Patients—In charts 1, 2, 3 and 4 are shown the clinical course of 4 typical patients and the corresponding serologic and bacteriologic studies done. Chart 1 shows the course of a patient who made an uneventful recovery, chart 2 illustrates the observations made on a patient in whom a purulent complication developed, chart 3 illustrates the course of a patient in whom a primary attack of rheumatic fever developed after a streptococcic infection and chart 4 shows the observations made on a rheumatic subject with 3 different group A streptococcic infections of the upper respiratory tract. The first

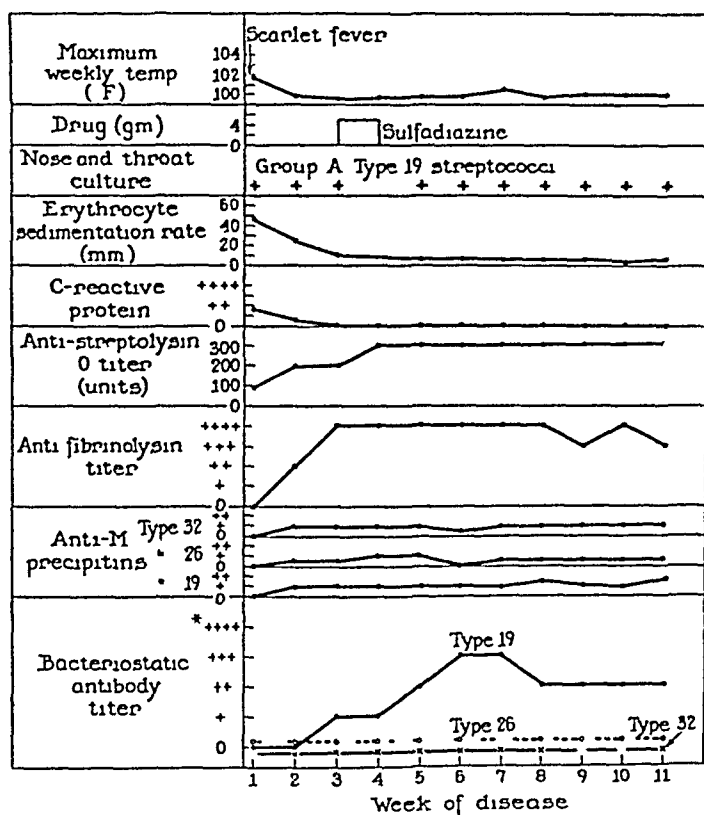


Chart 1—Course of a patient with an uncomplicated streptococcic infection of group A type 19

*+, ++ and +++ represent significant bacteriostasis of streptococci in culture dilutions of 10^6 , 10^5 and 10^4 respectively, 10^6 usually represented 200 to 300 colonies per cubic centimeter

infection in the last patient was uncomplicated, but the second and third resulted in recurrent attacks of rheumatic fever. Certain points are noteworthy in all these charts: (1) the persistence of hemolytic streptococci in the nasopharynxes of the patients, (2) the close correlation of the increased erythrocyte sedimentation rates with the presence of the C-reactive protein in the serum, (3) the cross reactions with the type-specific M protein extracts, (4) the type specificity of the bacteriostatic test and the long period for which the bacteriostatic antibodies

were present, and (5) the special importance of the determinations of antistreptolysin O and the bacteriostatic tests in patients with reinfection by different serologic types of group A streptococci

Multiple Streptococcic Infections—In 11 of the 153 patients more than one group A streptococcic infection developed. Ten were known

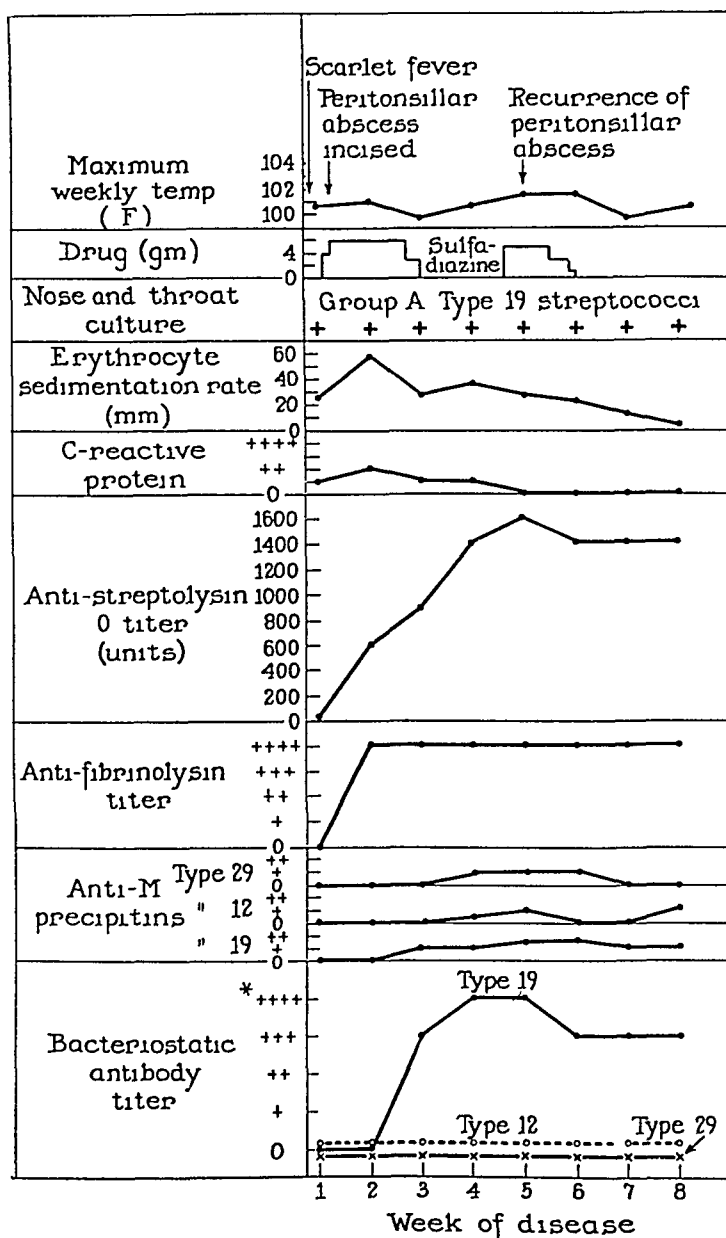


Chart 2—Course of a patient with a purulent complication following group A type 19 streptococcic infection

*+, ++, +++ and ++++ represent significant bacteriostasis of streptococci in culture dilutions of 10^0 , 10^5 , 10^4 and 10^3 respectively, 10^0 usually represented 200 to 300 colonies per cubic centimeter

rheumatic subjects, and 1 was a normal sibling of a brother with rheumatic disease. In 3 of the patients 3 separate infections developed, and 2 developed in 8 others. In 10 of the patients different known types of hemolytic streptococci were cultured from the nasopharynxes in each infection but in 1 patient with three separate attacks of disease of

the upper respiratory tract the streptococci could not be typed with the available serums by the precipitin technic although there were definite clinical findings and antibody responses in each of these infections. However, during 1 of the 3 infections, an indication was obtained that the strain was different from the others because bacteriostatic antibodies specific for this strain appeared in the patient's serum. The patients

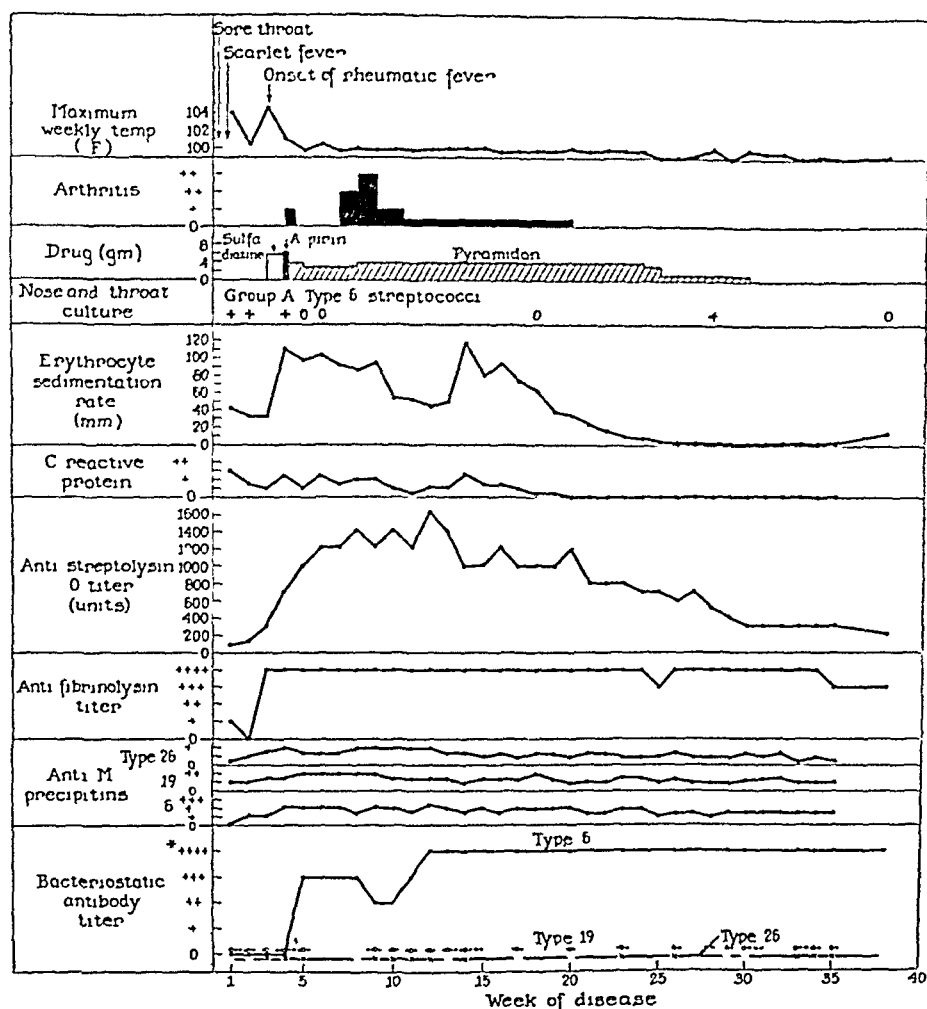


Chart 3—Course of a patient who had a primary attack of acute rheumatic fever after a group A type 6 streptococcal infection

*+, ++, +++ and ++++ represent significant bacteriostasis of streptococci in culture dilutions of 10^6 , 10^5 , 10^4 and 10^3 respectively, 10^6 usually represented 200 to 300 colonies per cubic centimeter

with multiple but separate infections of the respiratory tract had a different type of streptococci with each infection

Of primary interest also in this study is the fact that many of the rheumatic subjects suffered a number of nonstreptococcal infections such as rubella, herpes zoster, bacillary dysentery, appendicitis, acute epidemic conjunctivitis (pink eye), pneumococcal pneumonia and infections

of the upper respiratory tract of unknown origin, but in no instance was rheumatic fever observed after these infections. In this respect our findings are in agreement with those of others³²

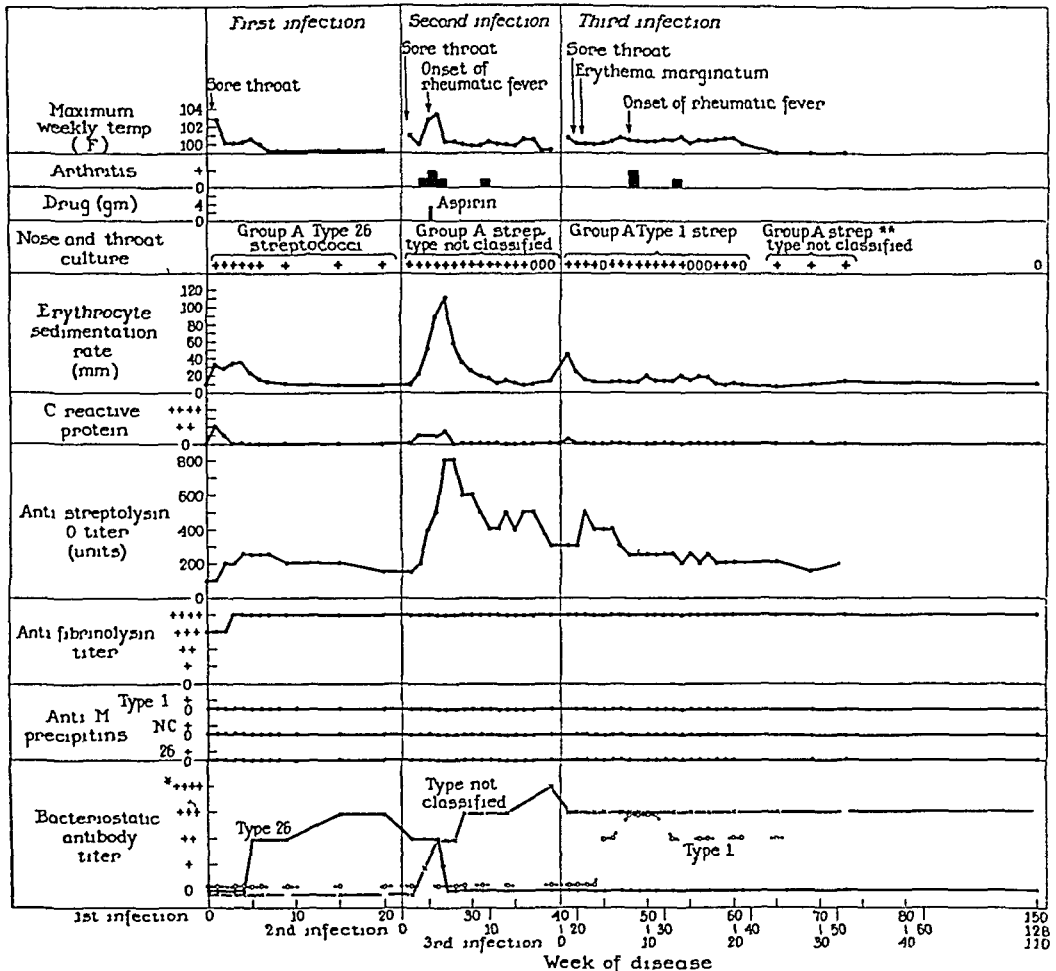


Chart 4—Course of a rheumatic subject with three different group A streptococcal infections

*+, ++, +++ and ++++ represent significant bacteriostasis of streptococci in culture dilutions of 10^{-6} , 10^{-5} , 10^{-4} and 10^{-3} respectively, 10^{-6} usually represented 200 to 300 colonies per cubic centimeter

**The streptococci of unclassified type comprised only a few colonies and were probably the same as those which caused the second infection

COMMENT

In order to determine whether there is any basic difference in the patterns of streptococcal antibodies in patients in whom rheumatic fever develops as compared with those who have purulent complications or

32 Reysersbach, G., Lerert, T. F., and Kuttner, A. G. An Epidemic of Influenza B Occurring in a Group of Rheumatic Children Concurrent with an Outbreak of Streptococcal Pharyngitis. Clinical and Epidemiological Observations, J Clin Investigation 20 289, 1941. Green, C. A. Epidemiology of Haemolytic Streptococcal Infections in Relation to Acute Rheumatism. III. Comparative Incidence of Various Infections and Acute Rheumatism in Certain Training Centers. J Hyg 42 380, 1942. Rantz, L. A., Boisvert, P. J., and Spink, W. W. Etiology and Pathogenesis of Rheumatic Fever, Arch Int Med 76 131 (Sept) 1945.

make uneventful recoveries after hemolytic streptococcal infections of the upper respiratory tract, the immunologic responses to a variety of antigens were studied in fairly large groups of patients. It is well known³³ that different strains and serologic types of streptococci vary in their antigenic composition and thus they may evoke different responses in the host. Moreover, persons are also known to respond differently to the same antigen.

The antistreptolysin O test gives the most satisfactory index of previous streptococcal infections probably because streptolysin O is an excellent antigen and the titer of this antibody can be accurately determined. The determinations of antifibrinolysin in this study were done before the quantitative method recently described by Kaplan²⁴ had been devised, and quantitative results were therefore not obtained. Because of its simplicity it was hoped that the anti-M precipitin test could be used for determinations of type-specific antibodies. It was found, however, that frequent and marked cross reactions with heterologous M extracts made this test an unreliable index of type specificity in patients' serums. Similar difficulties were encountered by Thomas³⁴. These reactions were not due to the group-specific C carbohydrate because this antigen had been eliminated from the M extracts. At present, the nature of these cross reactions is not understood, and the precipitin test as performed probably did not give a reflection of the type-specific antibodies in the patients' serums. The most reliable method for determining such antibodies was found to be the bacteriostatic test. In contrast to the anti-M precipitin test, no cross reactions were observed.

Since the antistreptolysin O reaction is the most sensitive test now available for detecting previous streptococcal infection, it was thought of interest to find out how often a rise in antistreptolysin O was accompanied with antifibrinolysin, bacteriostatic and anti-M precipitin responses. The data, obtained on 71 patients who had 83 group A strep-

33. Bailey, J. H. The Types of Hemolytic Streptococci Found in Scarlet Fever Patients and in Throats of Grammar-School Children, *Am J Hyg* **29** 107, 1939. Colebrook, L., Elliott, S. D., Maxted, W. R., Morley, C. W., and Mortell, M. Infection by Non-Hemolytic Group A Streptococci, *Lancet* **2** 30, 1942. Lancefield, R. C., and Stewart, W. A. Studies on the Antigenic Composition of Group A Hemolytic Streptococci. II. The Occurrence of Strains in a Given Type Containing M but No T Antigen, *J Exper Med* **79** 79, 1944. Herbert, D., and Todd, E. W. The Oxygen-Stable Haemolysin of Group A Haemolytic Streptococci (Streptolysin S), *Brit J Exper Path* **25** 242, 1944. Studies on Streptococcal Fibrinolysis. V. The in Vitro Production of Fibrinolysin by Various Groups and Types of Beta Hemolytic Streptococci, Relationship to Antifibrinolysin Production, Commission on Acute Respiratory Diseases, *J Exper Med* **85** 441, 1947.

34. Thomas, R. A. Precipitation and Agglutination Tests with the Hemolytic Streptococcus. Titration of "M" and "T" Anti-bodies in Human Sera, *Science* **100** 552, 1944.

tococcic infections, are summarized in table 5. Sixty-four of the 83 infections (77 per cent) induced a significant rise in the antistreptolysin O titer. During 14 of these 64, it was impossible to learn whether additional antifibrinolysin appeared because of the limitations of the method used, a rise in antifibrinolysin was observed during 40 of the remaining 50. In 45 of the 64 there was a rise in bacteriostatic antibodies. In 42 anti-M precipitins developed, but the significance of this finding is not clear, since in 32 of these cross reactions were observed. On the other side of the picture, in 16 of the 19 infections in which antistreptolysin O was not increased there was a rise in the bacteriostatic antibodies, in 1 of the remaining 3 there was an antifibrinolysin response, and in 2 anti-M precipitins developed. From these results it can be seen that antibodies directed against one or several of the various antigenic components of group A streptococci appeared in the serums of all the patients after the infection. Moreover, in 50.5 per cent of the

TABLE 5—*Correlation of the Antistreptolysin O Response with Antifibrinolysin, Bacteriostatic and Anti-M Precipitin Reactions in Serums from Patients with 83 Group A Streptococcic Infections of the Upper Respiratory Tract*

Antistreptolysin O	Positive 64			Negative 19		
	Positive	Negative	Not Determined	Positive	Negative	Not Determined
Antifibrinolysin	40	10	14	6	7	6
Bacteriostatic antibodies	45	19		16	2 (1)*	
Anti-M precipitins	42 (32)†	22		11 (7)†	8	

*Figure in parentheses indicates that in one additional infection bacteriostatic antibodies could not be determined because streptococci isolated from the patient did not grow in whole blood of normal children even without addition of test serum.

†Figures in parentheses indicate the number in which reactions with heterologous M antigens were also present.

83 infections three different antibodies, directed against streptolysin O, fibrinolysin and the type-specific M protein, appeared in the patients' convalescent serums.

Our findings are in accord with those of previous observers, who found that group A streptococcic infections of the upper respiratory tract precede the development of rheumatic fever. By means of immunologic studies, it is usually possible to establish the cause of the precursory pharyngitis in rheumatic patients as group A streptococci, although these micro-organisms may not be found on culture, the chances of obtaining this positive immunologic evidence are increased in proportion to the number of different antibody tests applied.

A comparison of the immune responses of the patients in whom rheumatic fever developed with those of the ones who escaped complications or sequelae or in whom purulent complications developed shows

that antistreptolysin O, antifibrinolysin, anti-M precipitins and type-specific bacteriostatic antibodies developed more frequently in rheumatic patients than in nonrheumatic ones. In the rheumatic group the maximal response of antistreptolysin O and the type-specific bacteriostatic antibody was delayed about two weeks as compared to that in the other two groups. When the average weekly bacteriostatic antibody responses of the rheumatic and nonrheumatic groups were reviewed, the former had an average lower response than the latter during each of the second to the fifth weeks. Whether these differences have significance with respect to the pathogenesis of rheumatic fever cannot at present be stated.

Mote and Jones^{1c} found that, compared to patients with streptococcal infections who recovered without sequelae, patients who had purulent complications as well as those in whom rheumatic fever developed exhibited a delay in the rise of antistreptolysin O. Coburn^{6b} also found a delayed antistreptolysin O response in patients in whom rheumatic fever developed after streptococcal infections of the upper respiratory tract, and he stated that this is characteristic. Because the grouping of our cases was not the same as that of these authors, direct comparison is not possible. In our series the beginning of the rise of antistreptolysin O was not delayed. These results are similar to those obtained by Kuttner and Krumwiede¹⁰. In our patients the maximal response occurred later in the rheumatic group than in the nonrheumatic group. Since the difference was not great and the number of patients in each group was small and since there were great individual variations within each group, it cannot be concluded from this study that a delayed appearance of antistreptolysin O is characteristic of the rheumatic patient.

Swift and Hodge^{6a} and Coburn^{6b} also reported a delayed response of anti-M precipitins in patients in whom rheumatic fever develops. The precipitin reactions which we obtained with M extracts and patients' serums were similar to those reported by these authors, however, in view of the numerous cross reactions observed, the significance of this reaction is not clear. On the other hand, the delayed response of the bacteriostatic antibodies, which is type specific, may be significant. As previously indicated, this applies to groups and not to individuals.

One of three factors may be invoked to explain the difference between rheumatic and nonrheumatic groups of patients.

- 1 The groups are too small and the differences too slight to have significance.

- 2 The administration of salicylates to the rheumatic patients may have delayed formation of the type-specific antibodies.

- 3 The average statistical differences may indicate that it is part of the nature of rheumatic fever to have a delayed type-specific streptococcal antibody response to group A streptococcal infections.

Several previous investigations indicate that salicylates may depress the formation of antibodies³⁵ In the present study, however, if salicylates had had this effect in the rheumatic group who had received them, it probably would have been reflected in the production of anti-streptolysin O and antifibrinolysin as well as of anti-M precipitins and bacteriostatic antibodies (table 3) This was not the case, for the production of antibodies was greatest in the rheumatic group The lag was evident only in the formation of type-specific antibodies It should also be noted that salicylates were not given to the rheumatic patients until the third to the fifth week after the onset of the streptococcic infections, hence the conditions were different from those in the aforementioned investigations³⁵ The observations would have been better controlled if a rheumatic group who were not receiving salicylates had been utilized, but for obvious reasons this was impractical

Such suggestions, as the figures herein presented may indicate, could only be brought out from an analysis of groups and not from the findings in any one person, especially when the manifestations of rheumatic fever may appear any time within a period of one to eight weeks after the precursory streptococcic infection Possibly with the development of further knowledge of streptococcic antigens and of new technics, these suggestions will lead to further exploration

SUMMARY AND CONCLUSIONS

1 One hundred and sixty-nine acute hemolytic streptococcic infections of the upper respiratory tract in 153 rheumatic and nonrheumatic patients were studied

A Group A streptococci caused 163 of these infections, group C caused 6 and group G caused 1 No cross infections occurred, and in no case did the same serologic type of group A streptococcus cause two separate infections in the same patient

B One hundred and two of the infections were uncomplicated, 29 were followed by purulent complications due to the same strain causing the original infection and 38 were followed by rheumatic fever Four of these 38 were also followed with purulent complications

C Rheumatic recurrences developed seventeen times (31.4 per cent) as a result of 54 streptococcic infections in 39 previously rheumatic subjects On the other hand, primary attacks of rheumatic

³⁵ Swift, H. F. The Action of Sodium Salicylate upon the Formation of Immune Bodies, *J. Exper. Med.* **36** 735, 1922. Derick, C. L., Hitchcock, C. H., and Swift, H. F. The Effect of Anti-Rheumatic Drugs on the Arthritis and Immune Body Production in Serum Disease, *J. Clin. Investigation* **5** 427, 1928. Homburger, F. Sodium Salicylate Inhibiting Anti-Rh Immunization in Animals, *Proc. Soc. Exper. Biol. & Med.* **61** 101, 1946.

fever resulted from 21 (18.3 per cent) of the 115 streptococcal infections suffered by 114 previously nonrheumatic subjects

D Rheumatic manifestations followed only those infections of the upper respiratory tract which were due to group A hemolytic streptococci, among these no special serologic type of streptococcus was found associated either with rheumatic fever or with purulent complications of the original infections. None of the 7 infections due to streptococci of groups C and G led to rheumatic sequelae, although 5 of these occurred in patients who had previously had rheumatic fever

2 Determinations of antistreptolysin O and antifibrinolysin were done weekly on all patients. Seventy-one of these patients (with 83 infections) were tested for other immune responses, i.e., type-specific bacteriostatic antibodies and precipitins against type-specific M, group specific C and streptococcal nucleoprotein. The serums of these 71 patients were also tested for C-reactive protein, and serums from 9 patients with rheumatic fever were examined for "phase" precipitins

A Significant rises of antistreptolysin O occurred in 77 per cent, of antifibrinolysin in 73 per cent, of bacteriostatic antibodies in 76 per cent, of anti-M precipitins in 64 per cent and of C-reactive protein in 71 per cent of the 83 infections. Similar results were obtained for the antistreptolysin O and antifibrinolysin titers of patients in the complete series of 153. No definite phase precipitins could be demonstrated in the 9 patients examined. Three different streptococcal antibodies were demonstrable in the serum of 50 per cent of the patients in the series of 83 infections, and one or more of the several antibodies investigated were found during convalescence in every patient

B The patients with rheumatic fever as a group exhibited rises in antistreptolysin O, antifibrinolysin and type-specific antibodies more frequently than did the group of patients who had purulent complications or who made uneventful recoveries. Patients with purulent complications, however, exhibited the greatest increases in antistreptolysin O titer

C A slight delay in the beginning of the rise of type-specific bacteriostatic antibodies and anti-M precipitins as well as a similar delay until the maximal level of antistreptolysin O was reached, was observed in the group of patients with rheumatic fever as compared with the nonrheumatic groups

3 From this study it is evident that at present no single pattern of antibody response can be used to diagnose the existence of rheumatic fever in any single person

THYMOL TURBIDITY TEST IN ACUTE INFECTIOUS DISEASES

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AND
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IN 1944 MacLagan¹ introduced the thymol turbidity test for diagnosis of diseases of the liver. With this test it should be possible to distinguish between hepatitis, obstructive jaundice and hepatic cancer. The thymol turbidity test has since been analyzed by various investigators (Watson and Rappaport,² Hawkinson and Giebenham, Shank and Hoagland,³ Kunkel and Hoagland,⁴ Lehmann,⁵ Maizels,⁶ Havens and Marck⁷ and Brante⁸). In conformity with MacLagan these investigators observed the reaction to be positive in about 90 per cent of cases of acute hepatitis and as a rule positive in chronic hepatitis, whereas it was rarely observed to be positive in cases of obstruction of the bile duct and hepatic cancer.

The thymol turbidity test is a flocculation reaction on certain plasma proteins. The flocculation occurs by means of a saturated thymol solution at pH 7.8. The turbidity is read in Pulfrich's photometer against a barbital buffer solution with thymol. The result may be indicated by the extinction value or converted into MacLagan's units.

The basis of the thymol test is by no means clear. Various writers have held that the positive reaction is due to certain changes in the serum globulin fraction, presumably the gamma globulin. These changes need not, however, be quantitative (MacLagan,⁹ Kabat, Hanger, Moore

From the Department of Infectious Diseases, Frederiksberg Hospital (Physician in Chief N. I. Nissen, M.D.), Copenhagen.

- 1 MacLagan, N. F. Brit J Exper Path **25** 234, 1944
- 2 Watson, C. J., and Rappaport, E. M. J Lab & Clin Med **30** 983, 1945
- 3 Shank, R. E., and Hoagland, C. L. J Biol Chem **162** 133, 1946
- 4 Kunkel, H. G., and Hoagland, C. L. Proc Soc Exper Biol & Med **62** 258, 1946
- 5 Lehmann, J. Nord med **25** 1364, 1946
- 6 Maizels, M. Lancet **2** 451, 1946
- 7 Havens, W. P., and Marck, R. E. J Clin Investigation **25** 816, 1946
- 8 Brante, G. Svenska lak tidskr **43** 2661, 1946
- 9 MacLagan, N. F. Nature, London **154** 670, 1944

and Landow¹⁰ and Brante⁸) By examining the thymol precipitate MacLagan¹ observed it to be a protein-thymol-phospholipid complex The thymol reactions became negative by ether extraction of the plasma This fact lends support to the view that the reaction may be due to changes in the lipid content of the plasma or in the lipid-protein complex Recant, Chargaff and Hanger¹¹ concluded from their experiments that a positive reaction to a thymol test is conditioned by an increased lipid content in the plasma, whereas the gamma globulin should play an inferior part

The fact that possible changes in the gamma globulins of serum might determine the result of the thymol test gave rise to the present investigation of the thymol test in acute virus diseases Treatment of measles

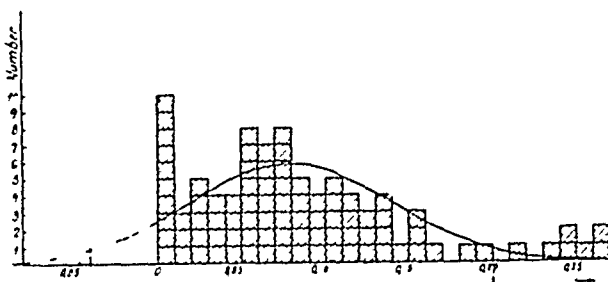


Fig 1—Results of the thymol turbidity test in 88 normal persons, 33 male and 55 female (Abscissa the extinction value, ordinate number of normal persons)

with gamma globulin during the incubation and at the initial stage of the disease is known to be able to alleviate or totally prevent the onset (Ordman, Jennings and Janeway¹² and Stokes, Maris and Gellis¹³) It has likewise been possible to reduce the incidence of the complicating orchitis in mumps by administration of gamma globulin extracted from serums of convalescent patients (Gellis, McGuinness and Peters¹⁴)

In addition to throwing light on these problems the present investigation gives information of the specificity of the thymol test and contributes to an elucidation of its value as a test of hepatic function

10 Kabat, E A , Hanger, F M , Moore, D H , and Landow, H J *Clin Investigation* **22** 563, 1943

11 Recant, L , Chargaff, E , and Hanger, F M *Proc Soc Exper Biol & Med* **60** 245, 1945

12 Ordman, C W , Jennings, C G , Jr , and Janeway, C A *J Clin Investigation* **23** 541, 1944

13 Stokes, J H , Maris, E P , and Gellis, S S *J Clin Investigation* **23** 531, 1944

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INVESTIGATIONS

Our material was composed of a collection of normal persons and of patients, the latter nearly all patients with acute infectious diseases admitted to the department for infectious diseases in the course of six months

The normal series comprised 88 normal subjects (55 women and 33 men) None of these had had hepatitis or recently any other infectious diseases

Figure 1 illustrates the distribution of thymol analyses concerning the 88 normal subjects The diagram is peculiar in having two peaks, one at an extinction value of about 0.07 and one at about 0 This leads to the supposition that a number of the values observed to be about 0 should actually have been negative

The theoretic distribution curve corresponding to the present material has been plotted (fig. 1) The mean value was observed to be 0.08

TABLE 1—*Thymol Turbidity Test in Different Acute Infectious Diseases*

Diagnosis	No of Cases	No with Positive Reactions	Percentage with Positive Reactions
Measles	45	32	71.0
Infectious mononucleosis	34	25	73.5
Tonsillitis	82	9	11.0
Streptococcic tonsillitis	29	4	13.8
Nonstreptococcic tonsillitis	53	5	9.5
Scarlet fever	73	4	5.5
Acute epidemic parotitis	31	2	6.5
Serous meningitis of unknown origin.	47	2	4.3
Smallpox	5	1	
Erythema multiforme	2	1	
Atypical exanthema	3	0	
Pneumonia	14	0	
Acute infectious hepatitis	12	9	75.0
Cerebrospinal meningitis	7	10	
Tuberculous meningitis	2	0	
Rheumatic fever	6	1	
Whooping cough	4	1	
Acute gastroenteritis	3	0	
Typhoid	2	1	

and the standard deviation 0.06 The upper limit of the thymol value for normal persons can be calculated as the mean values plus twice the standard deviation The upper limit should thus be 0.20

As appears from the curve, there is some divergence between the actual and the theoretic distribution as to the high values By calculating the normal values as the mean plus twice the standard deviation, 5 per cent of the normal subjects are seen to present a pathologic condition In the present series, however, 8 per cent fall outside the theoretic distribution curve This is probably due to the fact that turbidity measurements generally are somewhat difficult, presumably because the flocculation does not occur uniformly each time Moreover, a few normal persons must be expected to present pathologic values in consequence of past unnoticed infections

The series of patients comprised 373 persons suffering from different acute infectious diseases, as is seen in table 1

Table 1 is based on 1,865 thymol analyses. Daily serial analyses were made on a number of the patients, especially those who had infectious mononucleosis, measles and mumps. In the patients with the other diseases, generally only a few analyses were made. Since establishment

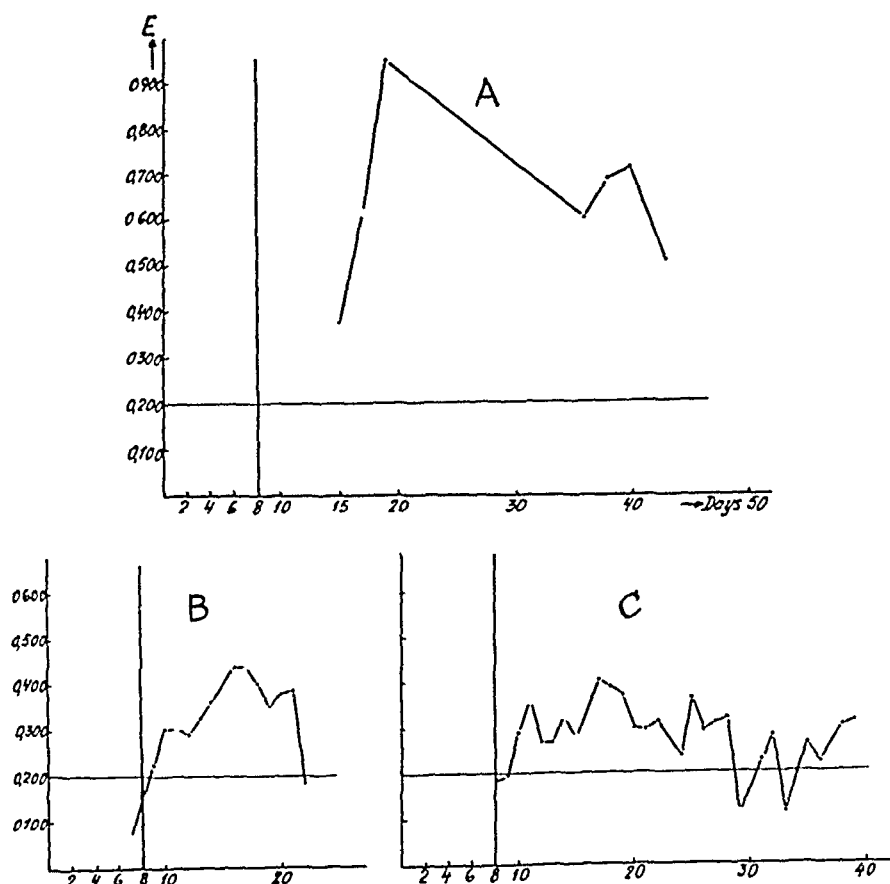


Fig 2.—Results of the thymol turbidity test in patients suffering from measles (Abscissa days of illness, ordinate the extinction value) The vertical line indicates the time of cutaneous eruption, the horizontal line indicates the normal upper limit (extinction 0.20) A, results in a 1 year old girl B, results in a 5 year old girl C, results in a 4 year old girl

of the upper normal limit is somewhat difficult, as is also the case in all other measurements of turbidity, a number of the normal results of thymol tests might be classed as presenting pathologic variations. This explains, no doubt, the few slightly positive reactions observed within the groups with mumps, scarlet fever and serous meningitis. The group with tonsillitis assumes an exceptional position in this respect, as will be discussed later.

The percentage calculation in table 1 is hardly an exact indication of the actual conditions, it must be somewhat arbitrary, because in some

cases only two analyses were made while in others numerous daily analyses were made

A detailed description of the condition within each group follows

Measles—A total of 45 patients were examined, of whom 31 were observed daily over a rather long period, maximally fifty-six days. The day of appearance of the eruption was for practical reasons fixed at the eighth day of illness. Analysis of the patients before the appearance of the eruption was possible in a few cases only. In the majority of the cases (71 per cent) the reaction to the thymol test began to be evident at the onset of cutaneous eruption and remained positive for greatly varying periods. In a few cases the reaction became negative by the

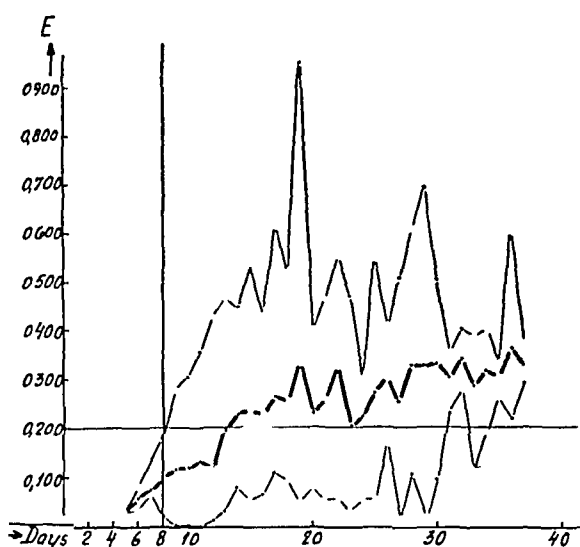


Fig. 3—The average curve of reactions to the thymol turbidity test in 42 cases of measles (the thick line). The upper and lower curves (thin lines) indicate the maximal and minimal values of the reactions to the thymol turbidity test during each day of illness. (The vertical line, at the eighth day, indicates the time of the cutaneous eruption.)

twenty-second day. The present material does not allow any conclusions as to the maximum period of positive reactions.

Of the 45 patients, 71 per cent presented positive reactions at one time or other within the period of investigation. Four patients, kept under observation for some length of time, never presented positive reactions.

Figure 2 shows typical curves for 3 patients with measles. The vertical line indicates the day of appearance of the eruption. It is hardly due to chance that the curve of reaction to the thymol test begins to rise simultaneously with the appearance of the eruption. As, however, we do not know the pathogenesis of the eruption, this problem will not be gone into further. Figure 3 illustrates an average curve for all 45 cases. The maximal and minimal values for each day of illness have been plotted.

at the same time. The test is less pronounced than in the case of acute hepatitis, yet decidedly positive in by far the greater number of cases.

Some tests of hepatic function were made in all the cases in which the reactions were highly positive (Takata-Ara reaction, urobilin, urobilinogen and icterus index according to the method of Meulengracht). All these tests gave a negative reaction. In none of these cases was the reaction to the Paul-Bunnell test positive.

Perhaps the thymol turbidity test may be of practical importance for the differentiation between measles and conditions with morbilliform eruptions of different origin (e.g., eruptions due to drugs).

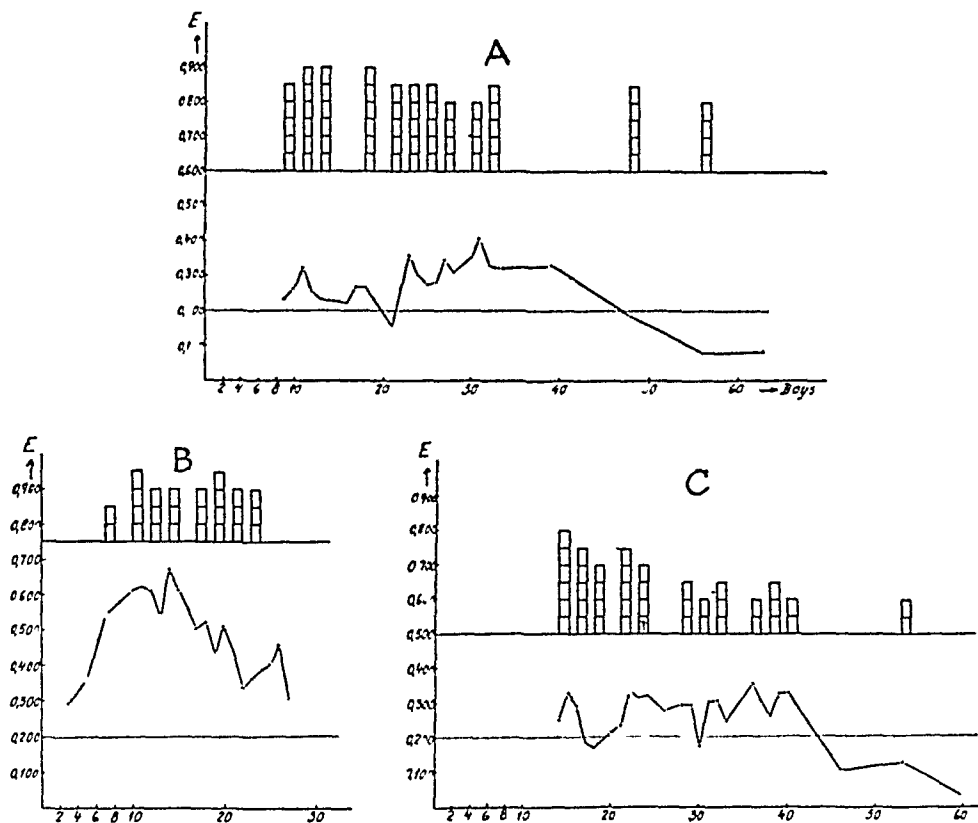


Fig 4—Results of the thymol turbidity test (curve) and the Paul-Bunnell test (columns) in patients with infectious mononucleosis. Each rectangle corresponds to agglutination in one tube. A, results in a 19 year old girl; B, results in an 8 year old boy; C, results in a 12 year old girl.

Infectious Mononucleosis—A total of 34 patients were examined, of whom 29 were observed daily over a rather long period, maximally fifty-five days. The criteria applied for the diagnosis were as follows (Thomsen¹⁵): (1) tonsillitis, (2) multiple peripheral glandular enlargements and (3) mononuclear cells in the peripheral blood of over 4,000 per cubic centimeter.

¹⁵ Thomsen, S. *Studier over mononucleosis infectiosa paa basis af 549 tilfaelde*, Thesis, Ejnar Munksgaards Forlag, 1942.

Since it is often difficult to fix the exact date of onset of infectious mononucleosis, the calculation of the days of illness is subject to some uncertainty. We calculated the days of illness from the day of onset of the tonsillitis. This is, however, somewhat arbitrary because the patients had often been feeling ill for one to two weeks before the onset of the tonsillitis.

As a rule the reaction to the thymol turbidity test is positive when the patient is admitted to the hospital with tonsillitis, which most often

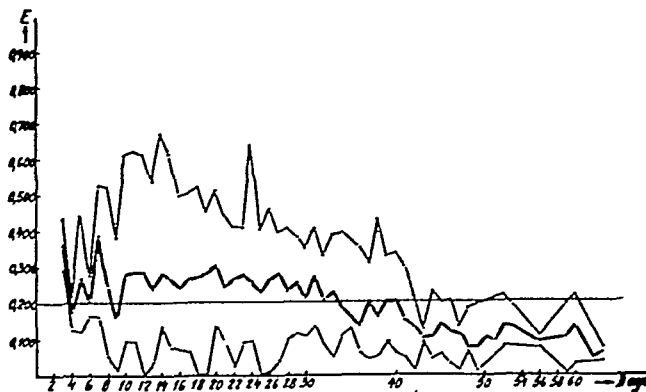


Fig. 5—The average curve of the reactions to the thymol turbidity test in 33 cases of infectious mononucleosis (the thick line). The upper and lower curves (thin lines) indicate the maximal and minimal values of the reactions during every day of illness.

occurs one to two weeks after the actual onset of the disease. None of the present cases was, for this reason, observed from the beginning.

Figure 4 shows three typical curves for reactions to thymol turbidity tests in infectious mononucleosis. It appears that the reaction curve

TABLE 2—*Reactions to the Thymol Turbidity Test and Paul-Bunnell Reactions in 34 Cases of Infectious Mononucleosis*

No. of Cases	Paul-Bunnell Reaction	Thymol Turbidity Reaction
20	Positive	Positive
6	Negative	Positive
7	Positive	Negative
1	Negative	Negative

may rise rather considerably. Figure 5 illustrates the course of an average curve for 33 patients, which shows that the reaction generally remains positive until the forty-second day.

A comparison was made between the reaction to the thymol test and Paul-Bunnell's reaction in all 34 cases of infectious mononucleosis. Paul-Bunnell's reaction was regarded as positive when there was agglutination in no less than four tubes.

It appears from table 2 that the reaction to the thymol turbidity test was positive in 26 cases of this not particularly large series, while the Paul-Bunnell reaction was positive in 27 cases. The reaction to both tests

was negative in 1 case only. Thus, if both tests are used it seems that the diagnosis can be made with certainty in nearly all cases.

There is no convincing correlation in degree between the two reactions, neither is there any correlation as to the time, although they both most often are positive immediately at the patient's admission. Yet we have seen cases in which the thymol reaction became positive prior to Paul-Bunnell's reaction and vice versa (fig. 4).

Tests of hepatic function were made in all cases to the same extent as previously mentioned, and only 1 patient proved to have complicating hepatitis associated with jaundice.

Tonsillitis—In dealing with the patients with tonsillitis we have distinguished between the following forms: (1) streptococcic tonsillitis, (2) nonstreptococcic tonsillitis and (3) tonsillitis in scarlet fever (table 1).

TABLE 3—Positive Thymol Reaction in Cases of Tonsillitis with Negative Paul-Bunnell Reaction (Presumably Cases of Infectious Mononucleosis)

Case No.	Age of Patient (Yr.)	Duration of Illness Prior to Admission (Days)	Peritonsillar Abscess or Enlargement	Streptococci in Throat	Thymol Turbidity Reaction	Results in Paul Bunnell Test (No. of Tubes with Agglutination)	Number of Mononuclear Cells	Comment
1	19	29	Present	Present	0.40	2	4,000	Presumably infectious mononucleosis
2	1	8	Present	Absent	0.85	0—2	10,050	Presumably infectious mononucleosis
3	2	2	Absent	Present	0.34	0—2	4,470	Probably not infectious mononucleosis
4	4	6	Absent	Absent	0.54	0—1	4,465	Probably not infectious mononucleosis
5	1½	7	Present	Absent	0.29	0	14,300	Presumably infectious mononucleosis
6	1	28	Absent	Absent	0.26	0—2	5,600	Presumably infectious mononucleosis

A total of 73 patients with scarlet fever were examined, two to four analyses being made in each case. The analyses were generally made between the third and the eighth day of illness. The reaction was observed to be positive in no more than 4 cases (5.5 per cent). As it was only slightly positive in these cases and as our normal series contained 8 per cent with supernormal values, we are justified in concluding that the reaction to the thymol turbidity test is not positive in scarlet fever.

Of the remaining patients with tonsillitis 82 were examined, among whom 9 showed a positive reaction to the thymol test. There was no difference in the frequency of positive thymol reactions between the cases with positive streptococcic observations and those with negative observations in the throat.

With this group, unlike the observations in the patients with scarlet fever, there were various patients with a highly positive reaction to the thymol test. A number of these patients were in all probability suffering from infectious mononucleosis, as will be shown.

After having reduced the number of cases of tonsillitis by these cases we found the incidence of positive thymol reactions within this group to be so small (6.1 per cent) that, as in scarlet fever, we could conclude that the thymol reaction does not become positive in tonsillitis.

The clinical data of 6 patients with tonsillitis with a highly positive reaction to the thymol test and a negative Paul-Bunnell reaction are illustrated in table 3. These cases, being of particular interest, will be analyzed further.

It appears from table 3 that the diagnosis in 4 out of the 6 cases might possibly be infectious mononucleosis. This diagnosis is supported by the long history before admission, which is typical for infectious mononucleosis, as well as the occurrence of peripheral adenitis and of increased amounts of mononuclear cells in the blood. It should be pointed out, however, that, of the 4 likely cases of infectious mononucleosis, in 1 peripheral adenitis was absent, while in 2 there was only moderate

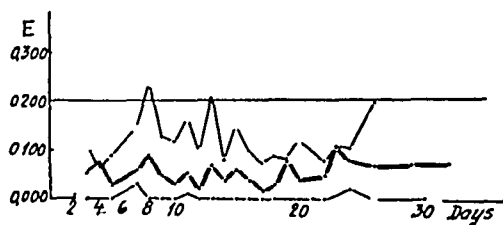


Fig. 6.—The average curve of the reactions to the thymol turbidity test in 25 cases of mumps (thick line). The upper and lower curves (thin lines) indicate the maximal and minimal values of the reactions during every day of illness.

monocytosis (i.e., less than 6,000 cells per cubic centimeter). Attention has been called to these cases, because we are of the opinion that the thymol reaction may contribute to the diagnosis in a greater number of cases of infectious mononucleosis, especially in children in whom the Paul-Bunnell reaction is often negative.

The practical importance of the facts stated here concerning the thymol test in tonsillitis and infectious mononucleosis lies in the possibility of distinguishing by means of this test between the two diseases on admission of patients.

Unfortunately, there were no cases of diphtheria among our patients in this period. It is therefore at present impossible to determine the significance of the thymol reaction for the important differential diagnosis of infectious mononucleosis and diphtheria.

Mumps.—A total of 31 patients were examined, most of whom had complications in the form of serous meningitis or orchitis. Ten were observed daily over a rather long period, maximally twenty-six days. Of the 31 patients only 2 (6.5 per cent) presented slightly positive reactions.

Figure 6 illustrates the average curve for all 31 cases, calculated for each day of illness. The maximal and minimal values for each day of

illness have been plotted at the same time. The average curve is seen to be within the normal range.

Serous Meningitis (Cause Uncertain)—Thymol analyses were made in 47 cases of epidemic serous meningitis. The disease is most likely nonparalytic acute anterior poliomyelitis, but the disease may also be caused by another unknown virus.

The reactions in only 2 (4.3 per cent) of the 47 cases were observed to be slightly positive. Hence we feel justified in concluding that the thymol reaction is not positive in this disease.

Other Infectious Diseases—A small number of thymol analyses were made for patients suffering from pneumonia, meningococcic meningitis, tuberculous meningitis, rheumatic fever, typhoid, erythema multiforme, smallpox, atypical exanthema, acute gastroenteritis and whooping cough. The reaction to the thymol test was observed to be positive in none of these patients, except in 1 of 2 patients with typhoid.

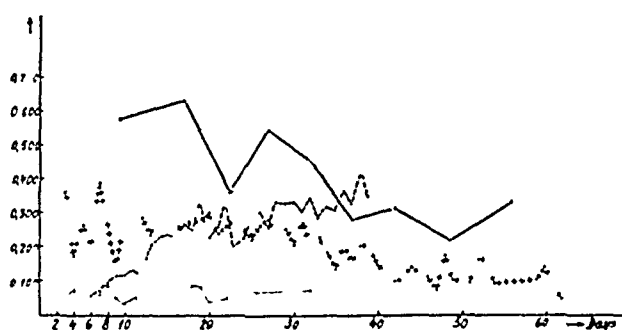


Fig. 7—The average curves of the reactions to the thymol turbidity test in acute infectious hepatitis (continuous line), measles (broken line), infectious mononucleosis (crossed broken line) and mumps (dotted line).

Finally, a diagram is presented in which a quantitative comparison is made of the reaction to the thymol test in acute hepatitis, measles, infectious mononucleosis and mumps. The curves are average curves, mentioned in order of succession, according to the strength of the reactions (fig. 7).

COMMENT

The fact that a positive reaction to the thymol test is seen not only in hepatitis but also in measles shows that a positive reaction is not exclusively a criterion of hepatic damage. It is well known that hepatitis never occurs in association with measles, and the tests of hepatic function never revealed signs of hepatic damage in our patients, although we observed even very high thymol values in a number of our patients with measles.

In infectious mononucleosis the positive thymol reaction indicates nothing certain, even though we found only 1 case of manifest hepatitis.

and never other signs of hepatic damage with the tests of hepatic function used Cohn and Lidman¹⁶ recently described 15 patients with infectious mononucleosis without jaundice, all of whom presented a positive thymol reaction as well as signs of hepatic damage according to the reaction to the sulfobromophthalein sodium test

It is therefore logical to assume that the thymol reaction in measles, infectious mononucleosis and hepatitis indicates certain changes in the serum globulins This may be directly connected with the antibody production Nothing can be said as to whether these changes in the serum globulins are of a qualitative or a quantitative nature

The curves for measles and infectious mononucleosis show that the thymol curve bears a certain resemblance to that for the antibody concentration in infectious diseases

Our investigations were started to determine whether the thymol reaction is positive in the virus infections in which here the gamma globulin has proved to have a curative or protective effect The fact that the reaction to the thymol test proved to be positive in measles and negative in mumps seems to be against the hypothesis that the thymol reaction alone may be an indicator of a change in the gamma globulins

On the other hand, the observation that in three widely different virus diseases a positive reaction to the thymol test can occur might tempt one to conclude that the reaction indicates the effect of a common antigen in the three virus forms This conclusion is, however, hardly justifiable on the basis of the present investigations

By way of summing up, we may say that the thymol test is hardly a test of hepatic function, but is rather to be regarded as an indicator of changes in the serum proteins in consequence of different virus infections

SUMMARY

An investigation has been made employing MacLagan's thymol turbidity test of 373 patients suffering from different acute infectious diseases The normal upper limit has been calculated as the mean value of 0.08 extinction plus twice the standard deviation, equal to 0.20 extinction

The reaction to the thymol turbidity test was observed to be positive in measles (71 per cent), infectious mononucleosis (73.5 per cent) and acute infectious hepatitis (75 per cent), whereas it was negative in tonsillitis, scarlet fever, mumps, serous meningitis, pneumonia, purulent meningitis, tuberculous meningitis and acute gastroenteritis

In measles the reaction becomes positive with the appearance of the eruption and remains positive for several weeks The thymol test pos-

16 Cohn, C, and Lidman, B. I. Clin Investigation 25: 145, 1946

sibly is of practical importance for the differential diagnosis of measles and other kinds of morbilliform eruptions

In infectious mononucleosis the reaction to the thymol test is generally positive at the time of the patient's admission and remains so for an average of six weeks. The thymol test may be employed as a supplement to the Paul-Bunnell test, since with both tests a positive reaction can be obtained in nearly all cases of infectious mononucleosis.

Since the tests employed by us revealed no signs of hepatic damage in association with infectious mononucleosis and measles, the thymol test must probably be regarded as a means of indicating changes in the serum proteins in consequence of the virus infections rather than as a proper test of hepatic function.

ADRENAL CORTEX AND ARTERIAL HYPERTENSION

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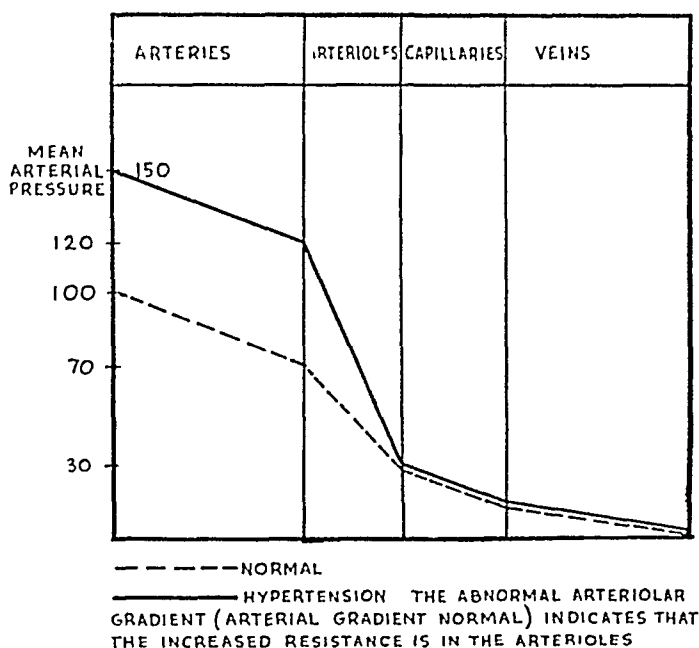
- A Introduction
- B Renal Hypertension
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 - Autopsy Studies
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A INTRODUCTION

Increased arterial blood pressure of known or suspected origin is an extremely common sign, listed in association with at least fifty-two diseases. Thus it is present in certain rare disorders of the endocrine glands, such as tumors of the adrenal glands or of the anterior pituitary gland (basophil adenoma). In cases of renal insufficiency there is a considerably elevated blood pressure. However, the fact remains that patients with these disorders constitute hardly more than 3 to 5 per cent of those with hypertension.

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Hypertensive vascular disease ("essential hypertension," Frank, 1911, hyperpiesia, Clifford Allbutt, 1895), including the malignant variety (Keith, Wagener and Kernohan, 1928) is far more commonly encountered than is high blood pressure due to all other causes and is now the leading cause of death, by far outstripping even cancer. Over 100,000 persons die every year in England and Wales from the effects of hypertension. Its origin and cure have been one of the persistent problems confronting physicians. Little is known about the underlying cause of this condition, though much has been learned about this type in the last few years. The employment of the word "essential" has been used to indicate ignorance of the cause of the condition.



Illustrating the site of increased vascular resistance in hypertension

Ideas concerning the etiology and the nature of chronic hypertension have been for the most part based on experimental work on animals and on clinical observations on human beings. There is good reason to believe that arterial hypertension is due to increased vascular resistance which is the result of widespread narrowing of the arterioles in the peripheral circulation and, to a slight degree or secondarily, in the pulmonary circulation and the right ventricle (Page and Corcoran, 1945).

In the majority of cases renal excretory function is not seriously impaired and the kidneys show little gross alteration in structure, though other renal functions of "hormonal" nature may be abnormal. Excretory and pressor-endocrine functions of the kidney are independent. After the arteriolar vasospasm has persisted for years, a diffuse hyperplastic vascular sclerosis (hypertensive vascular disease) results, which

is eventually responsible for failure of such organs as the heart, brain and kidneys

Among the causes of the disease that have been advanced are (*a*) a primary disturbance in the vascular system, (*b*) abnormal endocrine secretion, (*c*) abnormal sympathetic discharge from the higher autonomic (hypothalamic) centers, or (*d*) the liberation of excessive amounts of a pressor substance produced by the renal epithelial tissue

One important fact realized in the field of hypertension is that hyperactivity of the nervous system is not the primary cause of arterial hypertension, although some do believe it may play a part. There is no evidence that the sympathetic system is important in the causation of hypertensive vascular disease. The operation of double thoracolumbar sympathectomy now in vogue must be regarded as a nonspecific symptomatic treatment of the disease (Gold, 1945). There is no doubt that the autonomic nervous system, with the central autonomic nuclei, plays a part in maintaining arterial blood pressure and in elevating or depressing it. It is possible that this neurogenic element is a factor in the early phase of hypertension, but it is reinforced or replaced later by a humoral mechanism. Most research has supported the view that a chemical substance liberated by the kidneys elevates the blood pressure, but there is a growing body of acceptable evidence against the concept of a primary renal "ischemic" origin of human hypertensive vascular disease.

The nervous system undoubtedly mediates in the demands of the body for quick changes in the distribution of the blood, but the slow changes are caused by humoral agents.

According to investigations in recent years, it is believed, as stated previously, that arterial hypertension is the result of narrowing of the arterioles (precapillary arteries) in major vascular fields. It is not due to changes in the blood volume, or to increased viscosity of the blood, and while powerful left ventricular contractions are necessary for its maintenance, they are not causal. The constriction of the peripheral vessels may ultimately result from various humoral mechanisms, "pressor" substances at present incompletely identified may circulate in the blood, cause narrowing of the arterioles and thus increase the blood pressure.

Experimental work performed in recent years has demonstrated that the adrenal cortex plays a role in the pathogenesis of hypertension. Certain of the more important aspects of this problem are reviewed here.

Some features of the anatomy and physiology of the adrenal glands will be described first to aid in the understanding of their function and of their relationship to other systems of the body.

The adrenal (suprarenal) glands are two small masses which in man lie at the upper poles of the kidneys. They attain their greatest weight,

about 6 Gm each, between the ages of 16 and 30 years. The glandular cortical portion is vital to the organism.

The cortex and the medulla are of distinctly different developmental origin and in effect have been regarded as two endocrine organs. The adrenal cortex, which is of mesodermal origin, develops from the wolffian ridge in common with the ovaries and the testes and is related embryologically to the cortex of the kidney. Accessory adrenal bodies, or adrenal "rests," consisting of cortical substance, are commonly present in the liver and other structures, e.g., Marchand's organ in the broad ligament near the ovary, which is almost constantly present.

The functions of the cortex and the medulla may be influenced by their intimate vascular relationships. The vascularity of the adrenal glands is such that more blood passes through them than any other organ with the possible exception of the thyroid. Senescent changes are found in the arterioles to these glands as in other organs in normotensive subjects. In hypertension the changes in the adrenal arteries rank third in frequency, after those in the spleen and kidneys (Page and Corcoran, 1945). These vascular changes may be of importance in view of certain recent work (Victor, 1945) to be described later. A significant feature of the adrenal veins is the longitudinal bundles of muscle, contraction of which can apparently block the blood flow from both medulla and cortex, thus regulating adrenal secretion. This phenomenon is not yet properly understood. The recent work of Trueta and others (1946) in diverting the renal blood flow from the renal cortex by appropriate stimulation of the nerves suggests further the importance of the study of the adrenal blood flow.

The adrenal cortex is stated to be abundantly supplied with nerve fibers, but little is known regarding the effect of nervous influences on this portion of the gland. Myelinated fibers are stated to be abundant in the nerves distributed to the capsule and the cortex, while none is said to occur in the medulla, which is richly supplied with unmyelinated fibers. Nerves in a cortical plexus are described as giving rise to networks about the cortical cell groups, and many fibers terminate in relation to cortical cells. Denervation is not believed to abolish cortical function.

Bennett (1940) has presented evidence that (in the cat) there is no innervation of the adrenal cortex, and he has pointed out that what others have called an extensive and intricate network of fine nerve fibers resemble closely the impregnated argyrophile connective tissue collagen fibers in his sections.

The adrenal cortex, like so many other endocrine glands, is under the influence of factors elaborated by the anterior pituitary gland. Regarding the relationship between these two glands and the blood pres-

sure, more detail will be given later in this work, but the following points may be mentioned here. After hypophysectomy in rats, the blood pressure falls rapidly in eight days, but the injection of desoxycorticosterone or of adrenocorticotrophic hormone raises the level almost to normal. The subnormal blood pressure in the hypophysectomized rat is therefore mostly due to the resultant insufficiency of adrenal cortex (Braun-Menendez, 1944). Hypophysectomy also causes a fall of the blood pressure of rats with "renal" hypertension, which can be restored to the original level by the use of purified adrenocorticotrophic hormone (Anderson, 1944).

The investigations of Selye over many years, described in a review article recently written by him (1946), suggest that some of the most important diseases of man, such as hypertension, nephrosclerosis and the rheumatic disorders, may result from endocrine reactions which occur with long-continued exposure of the body to stress. Various noxious agents elicit pathologic and biochemical changes in the organism which are always the same irrespective of the stimulus. The sum of these nonspecific adaptive reactions is called by him the "general adaptive syndrome." During this syndrome, certain hormones of the anterior pituitary gland and the adrenal cortex are produced in excessive amounts as a defensive endocrine response, and these may become the cause of certain cardiovascular, renal and joint disorders, i.e., diseases of adaptation. These views of Selye will again be referred to, they have received widespread publication and consideration.

The role of the adrenal glands in the production of hypertension is thus by no means limited to the discharge of epinephrine. The significance of the cortex, pointed out long ago by Josue and Pilliet, is beginning to receive more attention.

Loss of function of the adrenal cortex, usually through tuberculosis or atrophy, results in Addison's disease, one striking feature of which is hypotension. No clinical condition has been attributed to overproduction of cortin, except with regard to the hormones responsible for some of the features in Cushing's syndrome (Albright, 1942) and the adrenocortical syndrome.

The association of hypertension with adrenocortical tumors is well established. One of the striking features of functioning "tumors" of the adrenal cortex is the variety and variability of the clinical pictures which they produce. The manifestations of hyperfunction vary remarkably from case to case, age, sex, mode of onset and quantitative and qualitative differences in hormone output determine the varied symptomatology and the termination of the disease. The differences in the clinical manifestations are not surprising, since the adrenal cortex is known from chemical studies to contain many factors, while clinical and experimental

evidence indicates that the cortex has several functions which in turn may not be related. Certain tumors give rise to pathologic masculinization due presumably to the production of androgenic substances. The cortex is important in metabolism and in the maintenance of sodium and potassium balance, the plasma volume and the blood pressure. It is important in the maintenance of the blood pressure in a case of hypertension, as it is in the animal with a normal blood pressure. Whether it is involved in "renal" hypertension in any other sense still awaits final proof. The relationship of adrenal cortex function to renal cortex function in the regulation of normal blood pressure and in hypertension will be considered in more detail later.

Nodular hyperplasia and excessive lipidosis of the adrenal cortex with or without medullary hyperplasia are frequently associated with hypertension. In man spontaneous tumors or hyperplasia of the adrenal cortex cells secreting desoxycorticosterone (or desoxycorticosterone-like substance) or corticosterone has not been recorded. These may exist. The adrenal glands are remarkably stimulated by exposure to diverse noxious agents. Selye (1936, 1946) has attempted to show how this stimulation affects the production of the salt-regulating or carbohydrate-regulating factor or influences some other unknown functions.

Certain qualitative and quantitative chemical and biologic procedures developed in recent years have made it possible to assess functions of the adrenal cortex not only in animals but in man.

In spite of many investigations on the function of the adrenal cortex, the intimate mechanisms underlying its activity remain obscure. Two ways of studying the function of such an endocrine gland, apart from such procedures as adrenalectomy, are (1) to determine the effect of its hormone on biologic processes and (2) to determine the conditions which affect the formation and liberation of its specific hormones, using a direct or indirect approach.

Thus direct determinations can be made of alterations of the hormone or its known metabolites in the gland itself, in the blood stream or in the urine. Indirectly, determinations can be made of the metabolic changes characteristic of the action of the hormone. Regarding hormone in the gland, estimations have not proved feasible owing to the low content of hormone in the gland at any one time. The level of the hormone in the blood has been studied by Vogt (1943 to 1945) and will be referred to again later. Urinary excretion products that may be estimated are as follows:

- 1 17-ketosteroids. These are not entirely an indicator of adrenal cortical hormone secretion.

- 2 "Cortical-like material" (urinary cortin). Weil and Browne (1939), Venning and Browne (1944) and Dorfman and his colleagues

(1942 to 1946) have shown by assay in rats that a variety of stresses increase the excretion of these hormones Lowenstein, Corcoran and Page (1946) recently described a chemical method for determining corticosteroids (both active and partially reduced)

Alterations in the cholesterol and ascorbic acid contents of the adrenal cortex appear to be associated with secretory activity of the gland These substances appear to be directly associated with the formation of cortical hormone (Long, 1946), cholesterol being the reserve steroid material from which the hormone is formed, to be excreted with ascorbic acid A wide variety of stresses, endogenous and exogenous, for example, cold, hemorrhage, burns, infections, drugs, may activate the adrenal cortex to secrete its hormone, as emphasized by Selye There is a fall in the cholesterol and ascorbic acid contents of the gland This response is believed to be produced through the anterior pituitary adrenocorticotrophic hormone

More detailed information on the morphologic, experimental and clinical investigations of the adrenal cortex will be discussed under appropriate headings in subsequent sections of this work in an attempt to show that abnormal function of this endocrine gland appears to be significant in the production and maintenance of hypertension

B RENAL HYPERTENSION, WITH SPECIAL REFERENCE TO THE ROLE OF THE ADRENAL CORTEX IN THE "RENAL PRESSOR SYSTEM"

Experimental Observations in Animals—Progress in the clinical investigation of hypertension has been made in recent years since it became possible to "reproduce" the disease in animals by constriction of the renal arteries or by compression of the renal parenchyma

In his classic experiments started in 1928 Goldblatt (1937) demonstrated that hypertension of great severity and of prolonged duration could be produced in the dog without loss of urea clearance by constriction of one or both renal arteries Adequate constriction of both main renal arteries either at the same time or at an interval caused persistent hypertension which lasted for years Similar results have been obtained by partial occlusion of the aorta just above the origin of the renal vessels Both the systolic and the diastolic pressure became elevated, in proportion, much as in human nephritis (Wood and Cash, 1936) Hypertension has been produced by the same method in other animals, for example, the monkey, goat, sheep, rabbit and rat, while recently Quinby and others (1945) have demonstrated that by constriction of the renal artery in man the renal humoral pressor mechanism is stimulated to activity as it is in animals Page (1939) has produced similar hypertensive effects in animals by wrapping the kidney in cellophane or

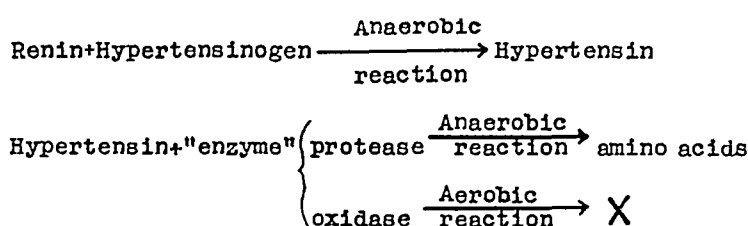
silk, the resulting aseptic perinephritis produces a fibrocollagenous hull around the parenchyma. This apparently causes hemodynamic alterations in the kidney which lead to the development of hypertension.

The experimental work of many investigators has suggested that the development of arterial hypertension associated with "renal ischemia" is due to a humoral mechanism in the kidney which is not dependent on the nervous system (the whole sympathetic system can be removed, yet the hypertension persists) or on the endocrine system with the possible exception of the adrenal cortex, which was considered at the least to be important in determining the degree of response.

Trueta and his collaborators (1946) have recently published interesting and important findings the implication of which may be far reaching. They have shown that in the experimental animal appropriate stimulation of the nerves may divert the renal blood flow from its commonly accepted course and that as a result the renal cortex may be partly or completely deprived of its supply, the blood being short-circuited through the medullary channels. Thus the suggestion has been made that hypertension may arise from abnormal activity of nerve centers from which impulses effect cortical ischemia and medullary congestion.

The production of experimental hypertension by compression of the renal artery is impossible in adrenalectomized dogs, and adrenalectomy is followed by a prompt fall in the blood pressure of dogs previously made hypertensive by clamping of the renal arteries. Goldblatt found that bilateral adrenalectomy abolishes the experimental renal hypertension and that the hypertension can be produced if even a minute portion of adrenal cortex is left or if the completely adrenalectomized animal is given cortical extract. Sustained hypertension can be produced even after the removal of one adrenal completely and the destruction of the medulla of the second, which indicates the importance of the cortical rather than the medullary portion in this connection. Blalock and Levy (1937), Page (1938) and Grollman (1940) also showed that the complete syndrome of experimental hypertension does not occur in the adrenalectomized animal. Dell'Oro (1942) reported that adrenalectomy produces an abrupt and marked decrease in the blood pressure of hypertensive rats, which can be only partially corrected by administration of desoxycorticosterone. Certain workers, however, were not able to confirm these results. Thus, Taquini (1938) found that implantation of an ischemic kidney in a dog with its adrenals removed causes permanent hypertension, and Rogoff and others (1939) concluded that neither cortex nor medulla plays a significant role in the causation of "renal" hypertension. Since so many independent investigators have found the contrary in large numbers of experiments, it is important that these workers point out where their experiments differ from those of the others.

Two explanations for the disturbance of hemodynamics produced in the kidney by the procedures mentioned have been (*a*) that the kidney is rendered "ischemic" (Goldblatt) or (*b*) that its blood supply is changed from a pulsatile to a continuous flow (Page). The latter view is the one now accepted. The disturbed circulation causes the liberation by the epithelium of the proximal convoluted tubules (and probably not by the cells of the juxtaglomerular apparatus of Goormaghtigh, as has been suggested by some authors) of a protein called renin. This acts in the blood stream on a renin substrate (α 2-globulin) called pre-angiotonin or hypertensinogen to form a pressor substance called angiotonin (Page and Helmer) or hypertensin (Braun-Menendez and his associates). The latter substance has been shown to have a vasoconstrictor action. It is gradually inactivated by blood and tissue enzymes called angiotoninase or hypertensinase, the level of hypertensin in the blood plasma depending on the relative velocity of its production and destruction (Cruz-Coke and others, 1945)



The renin substrate hypertensinogen is a globulin formed in the liver and possibly in the adrenal cortex. It decreases and even disappears from the systemic blood of untreated adrenalectomized male dogs (Lewis and Goldblatt, 1942, Houssay and Dexter, 1942). Adequate therapy with adrenal cortical hormone or with desoxycorticosterone results in a return of the level of hypertensinogen to normal. However, before attributing to the adrenal cortex an influence in the formation of hypertensinogen, the possibility should be eliminated that the low blood pressure of untreated adrenalectomized dogs, through liberation of renin by the kidney (Huidobro and Braun-Menendez, 1942), is not the cause of the disappearance of hypertensinogen from the blood.

Bilateral adrenalectomy and other procedures are reported to cause no change in the sensitivity of dogs to the pressor action of hypertensin (Houssay and Dexter, 1942). Several workers have shown that bilateral adrenalectomy decreases the response to injections of renin (Page, 1939, Williams and others, 1939, Friedman and his associates, 1940, Remington and others, 1941, Swingle and Remington, 1944). Bilateral adrenalectomy also prevents the appearance of a substance like angiotonin in the blood when experimental hypertension is produced in the dog by injection of kaolin into the cerebral ventricles.

Recently, Gaudino (1945) concluded from his experiments on rats that the presence of adrenal cortex tissue or of one or more of its hormones (desoxycorticosterone or 17-hydroxy-11 dehydrocorticosterone) seems necessary for the existence of renal hypertension and for the maintenance of normal arterial pressure. Thus in hypertensive adrenalectomized rats, administration of desoxycorticosterone and especially of 17-hydroxy-11-dehydrocorticosterone reestablished hypertension, cortical extracts (in the doses used) produced little or no effect.

Goormaghtigh has described a granular reaction and an increase in the number of the afibrillary cells in the kidney in long-continued hypertension caused by interference with the renal circulation. Removal of the kidney did not abolish the hypertension, it was suggested that an extra-renal factor is responsible for the raised pressure (editorial, *Lancet* 2 747, 1945).

Kottke and others (1945) were able to produce severe long-standing hypertension in dogs by appropriate renal artery-nerve stimulation, which persisted as long as the stimulation was maintained, however, as elevation of the blood pressure was not observed in anesthetized animals, they inferred that the hypertension is not due to the simple hemodynamic effects of renal vascular constriction.

Pickering (1945) concluded that during the first week after constriction of the renal artery in the rabbit hypertension is due solely or chiefly to the release of a humoral agent, probably renin, from the "ischemic kidney." Later a new and nonrenal factor plays an important and perhaps the chief role in maintaining the raised pressure.

The adrenal cortex is controlled by the anterior pituitary gland. Rats made hypertensive by partial ligation of one renal artery were hypophysectomized completely, this caused a fall of the blood pressure but not to a normal level except in those animals in which the hypertension had been present less than one month. A purified adrenocorticotrophic hormone preparation restored the renal hypertension to the level present before hypophysectomy.

After the production of experimental renal hypertension in rats hypophysectomy or adrenalectomy causes a fall of blood pressure, in some cases to below normal. The hypertension may then be partially, though rarely completely, restored by administration of desoxycorticosterone or of adrenal cortex extracts. Steroids such as progesterone, testosterone or estradiol did not raise the blood pressure in such animals in the experiments of Page and others (1946).

The failure to prevent completely the drop in systolic blood pressure following hypophysectomy in normal rats or in adrenalectomized hypertensive rats by replacement therapy with adrenal cortex extract or desoxycorticosterone suggests that either (a) the dosage or method of

administration has been inadequate or (*b*) there is some factor other than desoxycorticosterone elaborated by the adrenal cortex that exerts an influence on the blood pressure

All the work so far described, which started with the first report by Goldblatt of a method by which experimental hypertension can be produced in animals by the application of suitable clamps to the renal vessels or the aorta, must now be viewed in the light of a recent report by Victor (1945) In experiments on dogs it was found that ligation of the vessels to one adrenal gland (the left) leads to a prompt rise of blood pressure from an average of 125 mm of mercury to levels of 225 mm or more This hypertension was sustained for several months up to the time of publication (March 1946) and is comparable with that produced by the Goldblatt method of constriction of the renal arteries Ogden and others (1948) have repeated and confirmed this work

Observations in Man Regarding the Renal-Pressor System—Morphologic evidence that hypertension is not necessarily secondary to renal disease was furnished by Castleman and Smithwick (1943) They investigated biopsy material obtained from the kidneys during operations for subtotal sympathectomy in hypertensive patients and discovered a considerable number of normal kidneys both on gross inspection and on microscopic examination Master and others (1943) also carried out renal biopsies in the course of splanchnic resections in 100 patients with hypertension They concluded that in more than half the cases morphologic evidence of renal vascular disease was inadequate as the sole factor producing the hypertension and that in many cases hypertension preceded the renal vascular lesion They thought that their observations were not in keeping with the conception that renal ischemia is the cause of hypertension in man Hypertension, although present more often than not in patients with intercapillary glomerulosclerosis, is not a necessary part of the clinical picture, when present, it is in all probability associated with the arterial nephrosclerosis which is commonly present in diabetes mellitus

Goldring and others (1941) found no evidence in their investigation of 60 hypertensive patients to warrant the contention that renal ischemia is the primary cause of hypertension Friedman and others (1941), reporting a parallel study, stated that it appears highly probable that renal ischemia, although present in the majority of their hypertensive patients, may well be a secondary or concomitant mechanism in the pathogenesis of essential hypertension Thus the renal ischemia found in the hypertensive patient may be only a local manifestation of a generalized vasoconstriction, sharing in the latter and possibly aggravating it but not primarily causing it

The efforts of Homer Smith (1943), through his own experiments and the work of others involving methods devised by him, proved that in many cases of hypertension not only is renal function normal but the flow of blood through the kidneys is not diminished

The hypertensinogen concentration of the plasma was found to be normal in patients with hypertension and in a case of Addison's disease but often significantly decreased in cases of hepatic insufficiency (Haynes and Dexter, 1943) Normal concentrations of hypertensinase have also been found in the plasma of patients with hypertension

Page (1940) demonstrated an excess of angiotonin-like vasoconstricting substance in the blood of patients suffering from "essential" hypertension and from "malignant" hypertension (rapidly progressing hypertensive vascular disease)

Gregory and others (1944) presented evidence to show that angiotonin is not involved in the pathogenesis of "essential hypertension," and Browne (1944) also stated the belief that this substance is not responsible for the hypertension of eclamptic toxemia Grimson, too, concluded that there is no incontestable evidence that the renal hypertensive mechanism initiates the so-called essential hypertension in man (1942)

An important investigation because of its direct approach is that of Dexter and Haynes (1944), who measured the amount of renin in the blood of various types of patients with increased blood pressure They found renin only when the blood pressure was rising acutely (1 case of eclampsia, 2 of severe preeclampsia and 1 of fulminating acute glomerulonephritis were studied) None was found in cases of mild toxemia of pregnancy, moderate acute glomerulonephritis and chronic hypertensive vascular disease of all degrees of severity They suggested that the renin pressor system may be involved only initially in the development of hypertension

Quinby and others (1945) have demonstrated that constriction of the renal artery stimulates a humoral pressor mechanism to activity in man as it does in animals

The view that a "renal" factor is the cause of hypertension has been less favored as the evidence for it has become more complex

The properties of renin suggest that it is normally concerned with the regulation rather than the maintenance of normal blood pressure, and the development of tachyphylaxis gives cause for doubt as to whether excess of renin can be responsible for a persistently elevated blood pressure

The Hypertensive Toxemias of Pregnancy (Preeclampsia and Eclampsia)—The frequency with which hypertension coexists with pregnancy has received increasing attention in recent years

Two common conditions are (a) pregnancy occurring in a patient with essential hypertension and (b) pregnancy "toxemia" occurring in a healthy woman and leading to preeclampsia and eclampsia

Since the work of Goldblatt was published, the latter conditions have come to be regarded by many as the same as that which is known in the nonpregnant state as "essential hypertension" Against this is the fact that eclampsia never occurs with hypertension except in pregnancy Tillman (1942) suggested that it represents the disease as it occurs in the nonpregnant subject plus additional disease directly due to the pregnancy, i e, that hypertension predisposes to the occurrence of toxemia during pregnancy However, Page (1938) transfused 400 cc of blood from each of several patients suffering from either eclampsia or preeclampsia into normal pregnant women, without causing a significant rise of blood pressure in any case That a humoral factor is concerned is shown by the fact that the vasospastic phenomena and the increased blood pressure are often reduced by the termination of pregnancy

Fishberg has written that in a small proportion of the cases the condition develops in women with an endocrine disturbance which resembles Cushing's syndrome in the nonpregnant state The women in these cases present obesity of girdle distribution, a pudgy face, stocky build and more or less hypertrichosis of male distribution, the pelvis being predominantly anthropoid rather than gynecoid (Fishberg, 1939) According to Williams and Harrison (1939), also, perhaps 10 per cent of cases of so-called essential hypertension present the features of the basophilic syndrome in some degree

By inducing experimental "renal ischemia" in pregnant dogs and rabbits, Dill and Erickson (1939) produced a picture closely resembling that in human eclampsia They concluded that some factor other than simple renal insufficiency must be concerned in the rapid and fatal course noted in the pregnant animals

As is true of hypertensive vascular disease in general, little is known about the pathogenesis of the acute hypertensive syndrome of pregnancy, and theories are legion

Browne (1944) considered that the hypertension of eclamptic toxemia cannot be due to the renin-hypertensin mechanism or to a primary renal ischemia from any cause whatever He stated the belief that the pressor mechanism in toxemia is a humoral and not a nervous one but that the pressor substance is not angiotonin (hypertensin), tyramine or epinephrine Dexter and Haynes (1944), who found renin in the blood in 1 case of eclampsia, 2 of severe preeclampsia and 1 of fulminating acute glomerulonephritis, suggested that the renin-pressor system may be involved only initially in the development of hypertension

In a more recent communication, Barnes and Browne (1945) considered toxemia of pregnancy a temporary disorder leaving no permanent lesion. They stated that preeclampsia and true eclampsia do not cause permanent vascular or renal damage. Not all obstetricians agree with these views (Greenhill, 1945).

Little research has been done on any possible relation between adrenal disorders and the toxemias of pregnancy. In a search for the causes of edema and hypertension in eclampsia, the adrenal cortex deserves attention. It has been deduced that the decidua cells of the maternal placenta may liberate a factor causing maternal hypertension by chemical means (Sapeika, 1943) in a humoral mechanism in which the adrenal cortex might play a part. Parks (1943) suggested that in the last trimester of pregnancy the extra cortical secretion from the fetal adrenal glands might cause a disturbance in electrolyte distribution. There is not at present any suitable method of measuring the excretion of metabolites derived from adrenal substances which regulate water and electrolyte metabolism. The maternal rather than the fetal adrenal glands would appear to be the possible offender (Venning, 1946). Smith and Smith (1945) concluded that preeclampsia and eclampsia are related to premature deficiency of the placental steroid hormones, this, they stated, results in the elaboration of a toxic substance, presumably in the decidua, which accounts for the eclamptic syndrome.

It has been claimed that the signs and symptoms of toxemia of late pregnancy are due to the retention of sodium chloride in excess in the extracellular tissues, with dehydration of the cells. The sodium ion is detrimental in pregnancy when sodium chloride and sodium bicarbonate are given in excessive amount. The injection of hypertonic sodium chloride solution in a nontoxic pregnant woman has produced an eclamptic syndrome (editorial note in the "1945 Year Book of Obstetrics and Gynecology")

C CHANGES IN THE ADRENAL CORTEX ASSOCIATED WITH HYPERTENSION IN MAN

The relation of the endocrine system to the level of arterial pressure is known to the clinician from his knowledge of hypotension in Addison's disease and of hypertension in Cushing's syndrome and in certain adrenal carcinomas.

The role of the adrenal cortex in the production or maintenance of hypertension has not been fully elucidated, but the possibility of its importance is suggested by the experimental work mentioned in the previous sections and by certain well known clinical and pathologic observations which are described in the following paragraphs.

Autopsy Studies—There is considerable anatomic evidence that hyperplasia or adenomatous change of the adrenal cortex is a frequent concomitant of arterial hypertension, the incidence of such morphologic change being greater than could be accounted for by the factor of age alone. The pathologic hypertrophy of the cortex may be diffuse or nodular in type. In adults, cortical hyperplasia occurs mostly as nodules, which are small, not exceeding the size of a pea. Such nodular hyperplasia is observed at autopsy in a variety of hypertensive conditions, especially in nephritis and atherosclerosis. In other hypertensive patients, however, there may be no evidence of cortical hyperplasia, the size of the adrenals being within normal range, adenomatous hyperplasia also occurs in the absence of hypertension.

Morphologic evidence suggests that the adrenals share some measure of responsibility for hypertension. Sarason (1943), in a study of the adrenal glands, found cortical enlargement, with an increased amount of lipid, in cases of hypertension, the change was more striking when the hypertension was associated with primary vascular disease and less striking when chronic glomerulonephritis or pyelonephritis was a feature. No explanation is available for these changes. No significant alterations were present in the series of cases of atherosclerosis. Philpot (1909) found the mean weight of the adrenals to be much greater in those who had "chronic nephritis" than in comparable patients of the same age group without hypertension.

Rinehart and his associates (1941) reported that adenomatous hyperplasia of the adrenal cortex was almost regularly found in association with hypertensive vascular disease. They described nodular hyperplasia as pathognomonic of the disease, based on the comparison of the adrenal glands in 26 hypertensive and 100 control subjects, and they claimed that hyperplasia of the cortex in hypertensive vascular disease is almost as definite as that of the thyroid in exophthalmic goiter. The mean combined weight of the adrenals was greater by 4.2 Gm in a group of patients with hypertensive vascular disease than in a control group. Hyperplasia was also noticed in 8 out of 9 cases of chronic pyelonephritis.

Dempsey (1942) was unable to confirm these findings, maintaining that hypertensive subjects have no greater incidence of histologic alteration in the adrenal cortex than subjects with normal blood pressure. His arguments would, however, carry more weight if they were based on a larger amount of material. Dublin (1943) also could find no constant relationship between structure and function of the adrenal cortex in the pathogenesis of hypertension. In the course of studies on excretion of 17-ketosteroids, Bruger and others (1944) could find no difference in the incidence of hyperplastic or adenomatous changes in the adrenal cortex of hypertensive and normotensive subjects. There are reports that

the size of the adrenal gland is not altered by a preexistent hypertensive state (Dempsey, 1942, Koehler, 1936)

In the most recent and most comprehensive series of cases reported, Russi and others (1945) found the incidence of benign adenomas of the adrenal cortex in 9,000 routine autopsies to be at least 1.45 per cent. Hypertension and diabetes occurred five times as frequently in persons with cortical adenomas as in the general group, and both diseases were frequently present in association with such a tumor. In relation to hypertension, the authors stated the belief that there is a direct effect of the cortical hormones on vascular tone, the hormones rendering a person more sensitive to renin.

There have been a few reports of notable bilateral hypertrophy of the adrenal cortex in children, some showed features of pseudohermaphroditism, and others were normal. In a case reported by Skelton (1945) there were signs of a vascular disturbance, extreme pallor ushered in the disease. In none of the reported cases was the blood pressure recorded.

Biopsy and Clinical Studies—The frequent association of adrenal tumors and hypertension was noted by Castleman and Smithwick (1943). In the course of splanchnic resections for hypertension in 100 selected patients eight adrenal tumors were found in 7 patients, six were cortical adenomas and two were pheochromocytomas which had not caused paroxysmal attacks of hypertension. The authors also concluded that the morphologic evidence of renal vascular disease in more than half the cases was inadequate as the sole factor producing the hypertension and that the hypertensive state antedated the renal lesion. Many years ago Oppenheimer and Fishberg (1924) also found cortical adenomas more common in hypertensive patients, and Aubertin and Ambard (1939) noted that of 8 persons with hypertension 4 had diffuse cortical hyperplasia and 3 others adenoma of the adrenal cortex.

Hypertension due to tumors of the adrenal gland is not a great rarity. The hypertension due to tumors derived from the medulla (pheochromocytoma or paraganglioma) is usually paroxysmal but may on rare occasions be persistent (case report in the *New England Journal of Medicine*, 1944), it is different clinically and is clearly due to periodic release of epinephrine from the abnormally proliferating medullary tissue. Of interest in this connection is the demonstration by Vogt that injections of epinephrine hydrochloride (in doses which may be liberated in the body when the splanchnic nerves are stimulated) produce an output of cortical hormone into the blood, there is a relation between the adrenal medulla and the adrenal cortex.

As far as the adrenal cortex is concerned, carcinoma or adenoma may cause hypertension which is generally associated with the other constitutional manifestations of the hormonal activity of the tumor. The ele-

vated blood pressure returns to normal after the removal of the tumor (Boyd 1940), for example, hypertension forming part of Cushing's syndrome or the adrenocortical syndrome has been cured in a number of instances by operation

The fact that tumor of the cortex produces chronic hypertension without impairment of renal function necessitates the consideration that hyperactivity of the cortex is concerned in the pathogenesis of hypertensive vascular disease and other conditions in which hypertension is a feature, in much the same way as diminished cortical function is accompanied with hypotension

In hypercorticoadrenalism (adrenogenital syndrome) due, for example, to tumors as well as in virilism, hypertension is often present and is not of the paroxysmal type. Tumor or hyperplasia in children may lead to the clinical picture known as pubertas precox, which in some instances is associated with hypertension. Several steroids have been shown to be capable of inducing persistent hypertension in rats. Since abnormalities in sterol metabolism are known to occur in patients with the adrenogenital syndrome, the hypertension of this disorder may be due to the elaboration of such steroids by the abnormal adrenal tissue.

In Cushing's syndrome, a disease which occurs at any age and even in young children (the youngest patient reported on was only 11 weeks old) the clinical picture is most often dominated by features other than the hypertension, the hypertension may however be extremely severe and even enter the malignant phase, with hypertensive neuroretinopathy and necrosis of the renal arterioles. At present it is widely accepted that both pituitary and adrenal mechanisms are probably involved, though cases in which the condition is associated with carcinoma of the thymus are not easily explained. Occasional cases in which there were no visible adrenal changes have been described, as in recent reports by Heinbecker (1944) and McLetchie (1944).

The most plausible explanation here is that the adrenal cortex produces excessive quantities of ketosteroid and other hormones, but without any anatomic changes. Those hormones which accelerate gluconeogenesis from protein are regarded as important by Albright (1942), Cushing's syndrome is thus regarded as a hyperadrenocorticism with respect to the "sugar hormone". It is interesting to note that the blood sodium as well as the blood glucose is increased in Cushing's syndrome and in cases of adrenocortical tumor while the potassium content is decreased. Albright, with his tentative theory implicating the adrenal cortex in Cushing's syndrome, offered no explanation for the hypertension. The hematologic manifestations of Cushing's syndrome have been shown to be similar to those of the initial reaction of the body to nonspecific damaging agents ("adaptation syndrome" of Selye), and it has been suggested that the

hormone alterations in Cushing's syndrome are similar to those in the early phases of the "adaptation syndrome" (de la Balze, Reifenstein and Albright, 1946) Selye's work on nephrosclerosis and hypertension in experimental animals is referred to later

Heinbecker expressed the opinion that the hyaline changes in the pituitary basophil cells described by Crooke are degenerative and always secondary to some other lesion, either adrenal hyperplasia or hypothalamic atrophy They are seen also in hypertension not clearly due to Cushing's disease He found incidentally that there was considerable occlusive disease of the renal vessels in 3 of 4 cases which he considered adequate to explain the development of hypertension, no observations on the adrenal vessels were reported

In a large majority of cases of Cushing's syndrome there is tumor (Oppenheimer, 1935) or hyperplasia of the adrenal cortex, and the condition can be cured by surgical intervention Thus in a case in which

TABLE 1—*Changes in the Adrenal Cortex in Association with Arterial Hypertension*

Author	Changes in the Adrenal Cortex
Philpot (1909)	Mean weight increased
Oppenheimer and Fishberg (1924)	Cortical adenomas more common in hypertensive patients
Aubertin and Ambard (1939)	Of 8 persons with hypertension 4 had diffuse cortical hyperplasia and 3 others adenomas
Rinehart and others (1941)	Adenomatous hyperplasia almost regularly found, also an increase of mean combined weight
Sarason (1943)	Cortical enlargement, with increased amount of lipid
Castleman and Smithwick (1943)	Among 100 patients with hypertension 8 adrenal tumors were found in 7
Russ, and others (1945)	Benign adenomas present in at least 1.45 per cent of 9 000 routine autopsies, hypertension and diabetes five times more common in persons with cortical adenomas

the condition was due to adrenal carcinoma remarkable improvement followed removal of the tumor, with a disappearance of the abnormal features, including the raised blood pressure (Silver, 1940)

In Cushing's disease, therefore, as in the adrenogenital syndrome there is evidence of adrenal dysfunction, with the production of abnormal steroids The estrogenic and androgenic action of the urine in patients with these diseases has been demonstrated and a variety of abnormal steroids isolated from the urine The development of the hypertension may be attributed to the action of these abnormal steroids The adrenal glands should be studied in every case by palpation, pyelography or perirenal insufflation of gas If the urinary excretion of 17-ketosteroids is greatly increased, surgical exploration is probably justified as an adrenal carcinoma may be present in spite of failure to demonstrate it clinically There is also the possibility that increased excretion of other substances from the adrenal cortex may occur in the urine, this is discussed in a later section

It has already been stated that in animals sustained experimental hypertension can be produced even after complete removal of one adrenal

gland and destruction of the medulla of the other gland De Courcy (1934) obtained successful reduction of the systolic and diastolic pressures which lasted for months by performing subtotal bilateral adrenalectomy in patients with hypertension, one fourth of one adrenal gland is fully sufficient for all demands of the normal person In a discussion on the surgical treatment of arterial hypertension, Paterson Ross (1940) admitted that there are grounds for removal of the adrenal cortex in man were it not for the danger of total adrenalectomy

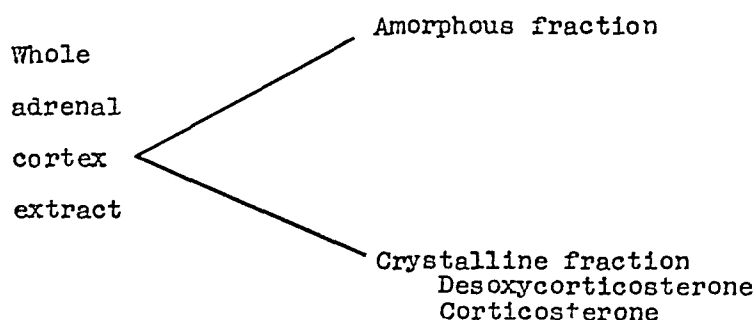
In table 1 is a summary of the changes found in the adrenal cortex in association with arterial hypertension

D ADRENAL CORTEX HORMONES AND THEIR FUNCTIONS

There are at present many theories concerning the functions of the adrenal cortex Conceptions differ as to what are primary functions and what are secondary effects dependent on such functions

The cortex is rich in globules of cholesterol esters and other fats In addition to steroids, there are a number of other compounds present in high concentration in the gland Sulfur is present, chiefly as glutathione Choline and vitamins (A, B₁, B₂ and ascorbic acid) are also present Long (1946) has recently brought forward evidence that cholesterol is the reserve steroid material from which "cortical hormone" is formed and then excreted with ascorbic acid

Until the actual hormones have been definitely established, it is unlikely that any final decision can be made Not all the hormones have been isolated, for the amorphous fraction which remains after the known crystalline steroid hormones have been removed from extract concentrates is extremely potent in its effect on the distribution of electrolytes it also maintains normal renal function and normal rate of growth



The elaboration and secretion of hormones by the adrenal cortex is controlled by the adrenocorticotrophic hormone produced by the cells of the anterior lobe of the pituitary gland As a matter of fact, it appears probable that there are three different pituitary corticotrophic principles which stimulate the androgenic "salt-active" and "sugar-active" hormones of the adrenal cortex (Selye 1944) During the "general adaptation syndrome" only the last two appear to be increased

It is important to observe that the various activities of the adrenal cortex are dissociable, as shown by the fact that the active substances isolated from the gland have many different physiologic actions

About thirty steroids have been isolated from the gland. Not all have been shown to have biologic activity. At least six compounds with "cortin-like" activity have been isolated as crystalline substances from extracts, though more will probably be found since the residue still contains half the original potency. Only one of these crystalline compounds, desoxycorticosterone, is available commercially.

The adrenal cortex contains substances which have estrogenic, progestational, androgenic and sodium-conserving functions, others which play a role in the intermediate metabolism of carbohydrate and protein and a derivative which is concerned with lactation. None of the isolated compounds possesses all these functions. The functions of the various steroids may be disturbed in different degree and various clinical disorders produced.

It is of interest that the administration of estradiol, progesterone, testosterone and desoxycorticosterone to normal rats induces an elevation of the blood pressure in some animals to hypertensive levels.

While it is true that adrenal cortex tumors can induce virilism, the stimulation of certain tissues in that condition is probably due to (a) excess of a certain cortical hormone or of a degradation product of it or (b) a metabolic variant with androgenic and other properties. As further evidence that the disturbance in virilism may not represent true adrenocortical overfunction is the attempt of Grollman (1936) to relate the activity of the adrenal glands in virilism to the function of a special inner "androgenic" zone distinct from the interrenal tissue or the cortex proper. In the mouse at certain stages there is a prominent zone of epithelial tissue, the juxtamedullary or X zone, between the medulla and the cortex proper which has a different character from the cortex and appears to be associated with sex. A similar zone is present in the human fetus, and Grollman claimed that virilism in the female results from resurrection of this tissue. Broster and Vines (1933) stated that the cortical cells of the male fetus present fuchsinophil substance from the tenth to the seventeenth week whereas this substance disappears much earlier in the female fetus. There is fairly convincing evidence that the gonadotrophic luteinizing hormone produced by the basophil cells of the hypophysis stimulates the adrenal cortex, probably the X zone, to produce in both sexes androgenic hormones similar to testosterone (Reifenstein, 1944). Levý Simpson has pointed out that in the adrenogenital syndrome the cells undergoing hyperplasia probably differ from those producing the "life-preserving" cortical hormone, since adrenal hypofunction (Addison's disease) may coincidentally complicate the picture, just as hypertension may be a feature of this syndrome.

In some circumstances certain cortical hormones necessary for the maintenance of normal blood pressure may be responsible in association with other factors for the production and maintenance of hypertension

Effect of Desoxycorticosterone in Man—Cortical extracts even in massive doses do not induce persistent or transient hypertension in either men or animals, probably because of the presence of numerous factors some of which may have opposite and regulatory actions

Overdosage with desoxycorticosterone, however, in the treatment of Addison's disease, especially when the salt intake is high, can cause hypertension, edema, rapid gain in weight, congestive heart failure and an increase in plasma volume, venous pressure and extracellular body fluid (Ferrebee and others, 1939, Soffer and others, 1940, Thorn and others, 1942, McGavack, 1941) Particularly noteworthy is the appreciable rise in diastolic pressure In some instances hypertensive levels may be obtained, without restoration of patients to normal activity (Ferrebee and others, 1939, Thorn and Firor, 1940, Cleghorn and others, 1939) Reduction of the dose of desoxycorticosterone and restriction of sodium intake will cause the hypertension to disappear

Perera and others (1944) found that in patients with Addison's disease and without adrenal disease there was progressive elevation of the blood pressure to levels above normal with prolonged administration of desoxycorticosterone The appearance of hypertension could not be correlated with abnormal retention of sodium, with an increased circulating blood volume or with an abnormally labile peripheral vascular system Loeb has suggested that since in some cases of Addison's disease the use of salt alone may elevate the blood pressure above normal the action of desoxycorticosterone may be merely due to an ion effect on the blood vessels Swingle and his co-workers (1941) have suggested that this steroid may perhaps affect the tone of the arterioles Certain other workers found that the elevation of the blood pressure following the administration of desoxycorticosterone could not be correlated with excessive retention of salt water in the circulating blood or with a labile vascular system as manifested by a positive reaction to the cold pressor test

It would appear from all the evidence that desoxycorticosterone acts directly or indirectly on the peripheral vascular system and that the hypertension induced by it is apparently a specific function of the hormone (Soffer, 1945), which is normally balanced by other fractions of the adrenal cortex

The profound effect on the blood pressure and the distribution of electrolytes warrant the routine use of this hormone in all suspected cases of the Waterhouse-Friderichsen syndrome (Weinberg and McGavack, 1945)

Effect of Desoxycorticosterone in Animals—Administration of desoxycorticosterone acetate has been observed to increase the blood pressure above normal levels in adrenalectomized dogs (Swingle and others, 1941, Remington and his associates, 1941), in normal dogs (Swingle and others, 1941, Kuhlman and others, 1939, Rodbard and Freed, 1942), in normal rats (Briskin and others, 1943, Grollman and others, 1940) and in hypertensive animals (Rodbard and Freed, 1942).

In the domestic fowl large doses of desoxycorticosterone cause nephrosclerosis, with hyalinization of the capillaries of the glomerular tuft, generalized tissue edema and cardiovascular changes (Selye, 1942). Large doses of sodium chloride added to their drinking water may be sufficient to elicit these changes (Selye, 1943). Selye and Hall (1944) administered excessive doses of desoxycorticosterone and sodium chloride to male rats and produced nephrosclerosis, renal arteriolar hypertrophy, hyaline casts in the renal tubules and pronounced cardiac hypertrophy. These findings suggest a possible causal role of adrenal cortical hyperactivity in the production of nephrosclerosis, "renal" hypertension and hypertensive heart disease in man.

Both desoxycorticosterone acetate (DOCA) and lyophilized anterior pituitary tissue (LAP) produce malignant hypertension, nephrosclerosis, polyarteritis nodosa of the cardiac vessels and myocarditis, lyophilized anterior pituitary tissue probably causes the adrenal cortex to elaborate desoxycorticosterone, like cortical hormones (Selye, 1946, Hall and others, 1946). Adrenalectomy prevents these effects. Selye (1946) advanced the theory that the spontaneous diseases of man such as those produced by overdosage of lyophilized anterior pituitary tissue and desoxycorticosterone are due to a defensive increase in the production of the adrenocorticotrophic and cortical hormones, the cardiovascular lesions being therefore by-products of this adaptive defence reaction, i.e., diseases of adaptation.

Grollman and others (1940) suggested that the hypertensive action of desoxycorticosterone is due to renal damage. Swingle and others (1941) and Leatham and Drill (1944), however, produced evidence against a toxic action on the kidney as a causative factor in the hypertension induced by this hormone.

Knowlton and his associates (1946) produced striking hypertension with use of desoxycorticosterone acetate in rats with cytotoxic serum nephritis, but no rise was observed in non-nephritic rats given the same doses of desoxycorticosterone or in nephritic animals which did not receive it. Administration of desoxycorticosterone caused a specific renal lesion in the tubules of all animals. The authors could not explain the mechanism responsible for the development of hypertension and the augmentation of the nephritic process.

From experiments on rats, Gaudino (1945) concluded that adrenal cortex tissue or its hormones (desoxycorticosterone, or 17-hydroxy-11-dehydrocorticosterone) are necessary for the existence of renal hypertension and for the maintenance of normal arterial pressure

Effect of Other Hormones—The pressor action shown by desoxycorticosterone is also exhibited by many other active hormonal substances. As a matter of fact, various commonly used steroids are capable of inducing hypertension in experimental animals. This suggests that the hypertension observed in certain endocrine disorders such as Cushing's syndrome and the adrenogenital syndrome may be due to the production of excessive amounts of normally occurring steroids or to abnormal steroid compounds.

It has already been mentioned that estradiol, testosterone, progesterone and desoxycorticosterone can produce hypertension in rats. It is of interest that the last two hormones and estrogenic and androgenic compounds are present in the adrenal cortex.

Daily intramuscular injections of diethylstilbestrol into normal rats or feeding with stilbestrol produced a gradual rise of systolic blood pressure, which reached hypertensive levels in many cases (Leatham and Dill, 1943, Grollman, 1940, Sapeika, 1948), this pressure response may be due to the adrenal glands, which were found to be much hypertrophied, or to an action on the kidney the function of which may be altered by steroids (Selye, 1939). The mode of action of large doses of stilbestrol in causing hypertension is not yet properly understood.

Estrogens in large doses inhibit anterior pituitary activity so that the signs of hypophysectomy are produced with the exception that the adrenal cortex does not atrophy and may actually become enlarged.

These effects which have just been described are produced in animals. In human beings, administration of estrogens often relieves the vasomotor and nervous changes at the menopause, and in the doses ordinarily used, doses far smaller than those (1 mg daily for a rat) administered to produce hypertension, it aids in restoring equilibrium and thus often reduces the blood pressure. The small doses of estrogen given for hypertension developing during the menopause is believed to act through inhibition of the anterior pituitary gland, overfunction of which occurs with the diminution of ovarian function, therefore any overfunction of the adrenal cortex at this time would also be indirectly inhibited by administration of estrogens. There are certain tumors of the ovary which produce excessive amounts of hormone, for example, the granulosa cell tumor which produces remarkably large quantities of estrogen, leading to precocious puberty and "feminization," and the arrhenoblastoma which produces large quantities of androgen. These do not appear to

cause any striking change in the blood pressure. A study of reports on these tumors failed to reveal any reference to the blood pressure levels.

Prolonged administration of large doses of diethylstilbestrol has been reported by Karnaky (1945) to produce no untoward effects except uterine bleeding. However, severe hepatic damage has occurred after moderate dosage (Elias and Schwimmer, 1945).

Estrogens in huge doses are reported to be of value in controlling toxemias of pregnancy in patients with diabetes mellitus.

a—c Bodies (Raab)—Raab (1941) has made determinations of adrenal hormonal compounds (epinephrine and cortical steroids, *a—c* bodies) in the human blood. The significance of such determinations is as yet not clearly defined. He could find no clear relation between the level of adrenocortical compounds and that of the blood pressure, but an abnormally high level of the compounds was found in a number of persons with renal hypertension. He found a much higher circulating level of adrenocortical compounds after muscular exercise in patients with essential hypertension than in normal subjects, and he regarded this tendency as the decisive factor in the development of arteriosclerosis and consequent ischemia of the vasomotor centers. Bruger and others (1944) stated that these *a—c* bodies do not increase quantitatively in the blood when the blood pressure is elevated during the cold pressor test in human beings or after the injection of renin in cats, there is, however, a close correlation between the rise in blood pressure and the concentration of *a—c* bodies in the blood of animals after the intravenous injection of epinephrine. In their study of these *a—c* bodies in normotensive and hypertensive human subjects they found the difference between the two groups to be statistically nonsignificant.

E URINARY EXCRETORY PRODUCTS OF ADRENAL CORTEX HORMONES AS AN INDEX OF ADRENOCORTICAL ACTIVITY

There are several methods for the determination of the potency of adrenal cortex extracts, based on the correction of physiologic changes which occur in the animal after adrenalectomy. For example, the profound changes in electrolyte metabolism, with short survival after the operation, markedly impaired muscle efficiency and hepatic gluconeogenesis, have been used as the basis for various methods of assay.

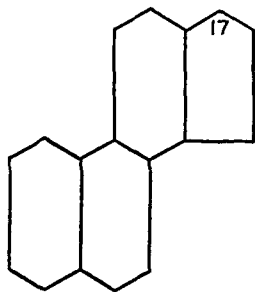
The adrenocortical hormones are rapidly inactivated in the animal body, and their excretory products are different from the original substances. Among the urinary steroids are androgens, estrogens and "cortins" and also physiologically inactive substances which in certain instances are more reliable as an index of hormone excretion than is the biologic activity found in urine.

In recent years it has been shown that certain aspects of adrenocortical activity in human beings may be measured by assays of certain urinary excretory products, corticoid substances and the 17-ketosteroids. The methods have proved useful but are not easy to perform.

It is recognized that excretion is not necessarily a measure of secretion and that increased hormone production may occur without an abnormally large amount appearing in the urine. However the extent to which the excretion of corticoid substances and the 17-ketosteroids, together or independently, will vary, may indicate possible types of adrenal secretion in various pathologic conditions. Selye (1946) pointed out that the immediate influence of certain stimuli, "alarming agents," is to eliminate the 17-ketosteroid and androgenic compounds present in the adrenal cortex together with the adrenocortical hormones (corticoids) but that later the gland produces only, or at least predominantly, adrenocortical hormones.

The concentration of ketosteroids in the urine as an index of adrenal cortex function is less specific than the concentration of cortin-like material since the gonads also may contribute to the total ketosteroid value. The partition of gonadal and adrenocortical hormonal derivatives of normal, endocrinopathic and cancerous patients has recently been reviewed by Salter and others (1946).

1 *The Urinary 17-Ketosteroids*—The significance of these recently discovered substances in the urine is still not fully investigated. These substances, whose exact precursors are not yet known, are excretory transformation products of the metabolism of steroids whose source is chiefly the adrenal cortex and the testis and are an index of the secretory activity of these endocrine organs. They do not possess measurable corticoid activity in the usual biologic tests. The term 17-ketosteroid (Callow, 1940) is applied in general to a group of compounds which give a certain type of color reaction and are so named because of a ketone group at the 17 position on the complex sterol molecule.

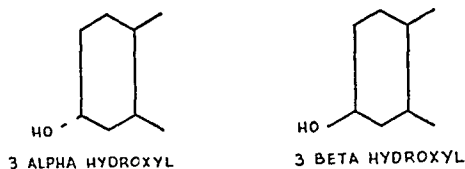


The terms 17-ketosteroid and androgen are often confused. Not all 17-ketosteroids are androgens, nor are all androgens 17-ketosteroids.

It is becoming increasingly apparent that the quantities of androgen or 17-ketosteroid excretion are measures less of testicular endocrine function than of the activity of the adrenal cortex (Callow, 1940).

The 17-ketosteroids are considered to be chiefly indicative of adrenal cortex activity because (a) they are lacking or present in only small amount in the urine in Addison's disease (Salter and others, 1946), (b) they are excreted in large amounts from certain active adrenal tumors and (c) they are excreted in nearly normal amount by castrated men and ovariectomized women, which demonstrates only a small contribution to their production by the gonads. It may be pointed out here that in cases of ovarian tumors, i.e., granulosa cell tumor and arrhenoblastoma, which produce large amounts of estrogen and androgen respectively, the output of 17-ketosteroid is normal. It has been estimated that a normal man excretes about 14 mg of 17-ketosteroids daily while the level for women is about 9 mg. Castration in the male reduced 17-ketosteroid excretion to the female level, while total loss of adrenal cortex function in Addison's disease decreases the level for both sexes to near zero. In cases of panhypopituitarism there is little or no 17-ketosteroid in the urine because of atrophy of both testes and of the adrenal cortex. Consequently the estimation has been made by Fraser and others (1941) that of the total daily excretion of 17-ketosteroids of 14 mg, 9 mg has its origin in the adrenal cortex in both sexes while 5 mg is derived from the Leydig cells of the testes and none from the ovaries. The daily fluctuations in normal circumstances are not great, so that one or two accurately timed and collected twelve-hour or twenty-hour specimens of urine are sufficient for most clinical diagnostic purposes (Talbot and Butler, 1942). Normal children under 7 years of age excrete negligible amounts of hormone (Talbot and others, 1940).

In certain diseases it appears to be valuable to separate the total neutral ketosteroids into alpha alcoholic, beta alcoholic and nonalcoholic fractions, as alterations in the ratio of these ketosteroids may exist. Procedures suitable for use in hospital laboratories have been described (Talbot and others, 1940 and 1941, Bauman and Metzger, 1940, Cahen and Salter, 1944). The terms alpha and beta refer to the spatial position of the 3-hydroxyl group (Fieser, 1937).



Available evidence indicates that whereas the alpha neutral ketosteroids probably arise from the adrenal and gonadal secretions, the beta neutral ketosteroids are an excretion product only of the cells of the adrenal cortex. They form a small percentage of the normal total daily output. The average values for normal persons as recently published (Salter and others, 1946) are as follows for the 3-cis (β) hydroxyl frac-

tion, 1.3 mg per day, for the female 3-trans (α) hydroxyl fraction, 6.3 mg per day, and for the male 3-trans (α) fraction, 12.9 mg per day

Unusually large amounts of the beta form are excreted in cases of adrenal tumor (Crooke and Callow, 1939, Talbot and others, 1942). Recent evidence suggests that only two beta 17-ketosteroids exist in significant amounts in the neutral fraction of urine extracts (Callow, 1939, Butler and Marrian, 1938). The first is dehydroisoandrosterone, an androgen present in small amounts in normal urine (Callow, 1939, Koch, 1937), and the second is isoandrosterone. The adrenal origin of dehydroisoandrosterone seems well established, and estimation of this substance in the urine might indirectly measure one function of the adrenal cortex. In most human subjects, normal or diseased, the role of dehydroisoandrosterone is relatively small, but it is of more significance in adrenocortical tumors (Salter and others, 1946).

Assay of urinary 17-ketosteroids may thus provide diagnostic information helpful in detecting hyperfunction or hypofunction of the adrenal cortex. In the urine of patients with adrenal hyperplasia and cortical tumors there are not only a great number of ketosteroids not found in normal urine but also a distinct difference in the pattern of their distribution. Evidence of chronic adrenocortical deficiency may be obtained from the biochemical picture of the blood, special diagnostic procedures, e.g., maintenance of a low sodium chloride intake, or decreased urinary 17-ketosteroids (Sharpey-Schafer, 1944, Reifenstein, 1944). In the adrenogenital syndrome grossly increased excretion of 17-ketosteroids or androgen favors the diagnosis of a tumor. In this condition the gland presumably secretes an abnormal product for reasons already given and also since the syndrome cannot be produced by the use of massive doses of cortical extract. In cases of masculinizing tumors values as high as 176 and 166 mg daily and even higher have been recorded (Talbot and others, 1940, Fraser and his co-workers, 1941, Talbot and others, 1941). In cases of postpubertal tumor the output may vary from 40 to 325 mg. or more per day ("British Encyclopedia of Medical Practice," 1944, p. 54, Scowen and Warren, 1946). In Cushing's syndrome the values are sometimes increased above normal.

Administration of desoxycorticosterone acetate to normal persons of either sex did not increase their excretion of 17-ketosteroid (Cuyler and others, 1942).

The fact that an excess of total 17-ketosteroids may be excreted daily in the urine of patients with adrenocortical hyperplasia or actual tumor in whom there is little or no elevation of the blood pressure and the fact that a "pressor" steroid like desoxycorticosterone causes no increase in the excretion of 17-ketosteroid, would suggest that estimation of these products can be of no help in determining the role of the adrenal cortex.

in the pathogenesis of hypertension Bruger and others (1944) found that hypertensive women (chosen because in them the entire amount of 17-ketosteroid excreted appears to be derived from the adrenal cortex) tend to excrete less 17-ketosteroids in the urine than normal subjects, which they suggested may indicate a hypofunctioning adrenal cortex in patients with hypertension, reflecting perhaps a gland exhausted under the constant strain put on it by the persistent elevation in blood pressure. Another explanation, based on Selye's work, is that the lowered ketosteroid excretion may represent a "shift" in the production of hormones by the adrenal cortex, while this gland produces excessive amounts of "corticoids," it may not be able to elaborate the normal quantity of "testoids." It has still to be demonstrated what the urinary output of other adrenocortical substances is in arterial hypertension.

It is possible that further characterization and identification of the urinary steroids will result in the discovery of compounds which will indicate some of the lesser known or unknown functions of the adrenal cortex.

2 Cortical-like Material—The "cortin-like" properties of extracts of urine from various sources have been demonstrated by several investigators. Thus, Dorfman and his associates (1942, 1944) have demonstrated that normal human urine contains adrenal-cortex-like material, a complex mixture of substances, which will exert a biologic effect similar to those of the adrenal steroids, when administered to adrenalectomized rats, the urine extract maintains life, protects the animals against death from cold and has glycogenic properties. The active material is in the ketonic neutral fraction, and at least a portion appears to be in a combined form. It does not give the color reaction for 17-ketosteroids.

Other workers have also demonstrated that extracts of urine contain cortical-like material (Perla and Gottesman, 1931, Grollman and Firor, 1932, Weil and Browne, 1939). Cortical steroid-like material has been shown to be present in greater amounts in the urine obtained from patients after operation (Venning and others, 1944) than in the urine of normal men. Cortin-like material could only be demonstrated once in samples of urine from 7 patients with Addison's disease (Dorfman and others, 1944).

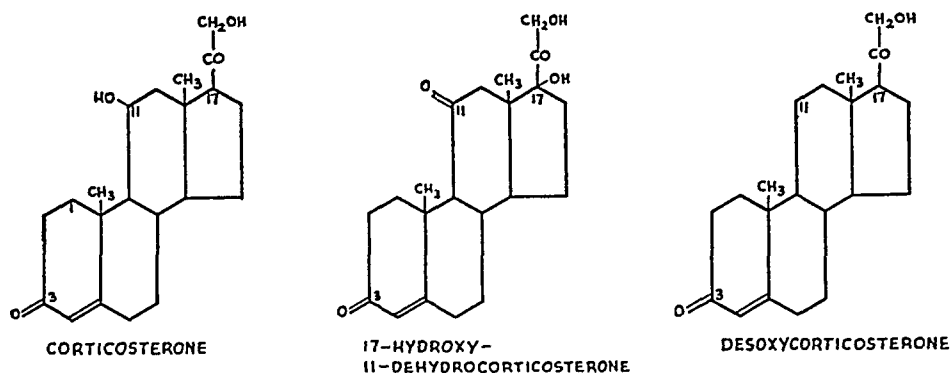
Vogt (1943) could not detect cortical material in the arterial blood of various animals or in blood from the right side of the heart, this indicates that the body disposes at great speed of the hormone released from the gland. She concluded that renal excretion plays a minor role in the disposal of cortical hormone. The liver, spleen and gastrointestinal tract were found to be unessential for this rapid inactivation of the hormone. An amount of cortical hormone detectable by biologic assay was, however, present in the venous blood leaving the adrenals, its quan-

tity being surprisingly high. As far as could be detected, the minute output by the adrenal cortex was not affected by changes in the blood pressure or in the blood flow. An injection of epinephrine greatly increased the output per minute of cortical hormone, and repeated injections caused an increase in weight of the adrenals associated with lipid storage, this did not occur after hypophysectomy (Vogt, 1944). The adrenal glands are extremely vascular, and the functions of cortex and medulla may be influenced by their intimate vascular relationships.

It seems justified, from the investigations of Dorfman and others, to conclude that the active urinary cortical-like substances are metabolites of adrenal cortex steroids and that variations in this urinary content reflect the physiologic activity of the gland. Although only incomplete data are available at present, the behavior of these substances on partition between various solvents and the possession of a reactive group relates them chemically to the known biologically active steroids of the adrenal cortex. Indirect evidence of the adrenal origin of these substances is provided by consideration of the amounts present in the urine in different circumstances. Thus the urine of man after exposure to stress, burns, infections and operations contains three to thirty times the amount of cortin-like material that is excreted by normal persons. In rats under similar conditions of stress the adrenal cortex loses its lipids and then hypertrophies, which indicates indirectly that there has been increased secretory activity. As pointed out previously, Selye (1946) stated that immediately after a stimulus (an alarming agent) 17-ketosteroids and androgens are eliminated together with adrenocortical hormones by the adrenal cortex but later the adrenocortical hormones are predominantly produced.

Few experiments have been reported on the detection of biologically active substances in the urine after the administration of adrenal cortex steroids. Some workers (Venning, Hoffman and Browne, 1944) have shown that approximately 10 per cent of the biologically active substances of an adrenal cortex extract injected intravenously in man and in the dog is recoverable from the urine.

Ready identification of the urinary corticosteroids may offer a new insight into the workings of the complex adrenal cortex factory. The urinary substances which have definite corticoid activity on biologic assay as measured by their effect on carbohydrate metabolism and muscle function are cortical steroids having an oxygen atom at position 11 on the steroid skeleton, e.g., corticosterone and 17-hydroxydehydrocorticosterone, whereas desoxycorticosterone is especially effective in maintaining the life of adrenalectomized rats, including those exposed to cold.



Recently, Dorfman and his collaborators (1946) showed by their assay method in rats that a pooled sample of male urine contained activity the equivalent of 0.6 mg of 11-dehydrocorticosterone per liter.

A new chemical method that estimates both active and partially reduced corticosteroids in urine has recently been published (Lowenstein, Corcoran and Page, 1946). The average excretion in normal males was found to be 0.5 to 0.8 mg per twenty-four hours, expressed as dehydrocorticosterone, a level of 0.15 mg was found in a case of Addison's disease and a level of 21 mg in one of Cushing's syndrome.

Comparison of Cortical-like Material and 17-Ketosteroids—The concentration of cortin-like material in the urine may serve, as already suggested, as a specific index of cortical function. These substances and a number of closely related steroids were first isolated from adrenal gland extracts and later demonstrated to be present in the complex mixture of substances extractable from the urine by the solvents.

Although variations in the excretion of 17-ketosteroids also to a certain degree reflect adrenal cortex activity, the parallelism is rather crude. These urinary 17-ketosteroids are different both chemically and biologically, e.g., androsterone, dehydroisoandrosterone, and androsterone-17. They typically lack the ketol side chain at C-17 characteristic of the hormonally active adrenocortical steroids and also lack the ketone group at C-3 (see formulas given previously). They contain 19 carbon atoms whereas the adrenal substances contain 21 carbon atoms per molecule. They do not possess measurable corticoid activity in the usual biologic tests. Their chemical constitution suggests that they are metabolic products of more active substances, i.e., they may be reduction products of corticosteroids. They are excreted as esters, detoxified material, whereas the active urinary "cortin" is apparently not conjugated or at least only a portion appears to be in the combined form. The 17-ketosteroids have still to be properly sorted out and the contributing sources identified. Their exact precursors are not yet known so that they may be considered as general indicators of adrenal cortex secretion rather than products of specific cortex hormones. These compounds

arise only in part from the adrenal glands, and in fact there may be additional sources other than the gonads

COMMENT

The Renal Pressor Mechanism—There is little doubt that after the constriction of one or both renal arteries a chemical agent, renin, is produced, which then leads to a state of hypertension. There has been much evidence of participation of the renal pressor system in the genesis of hypertension, but there is also evidence from certain studies in both animals and human beings at variance with this belief (Goldblatt, 1947). The initial cause for the secretion of this chemical substance in arterial hypertension itself and the nature of the chemical agent have not yet been clearly demonstrated. Renin appears to be normally concerned with the regulation of blood pressure rather than with the maintenance of normal blood pressure. The presence of the components of the renal pressor system, renin, renin activator and renin inhibitor, in normal subjects suggests, on teleologic grounds, some function of this system in normal physiology.

The development of tachyphylaxis to this substance renin without the occurrence of a corresponding decrease in arterial pressure makes it doubtful whether it can be responsible for a persistently raised blood pressure. In hypertensive vascular disease, careful search has failed to reveal the reason for the elevated diastolic pressure, the cause for the generalized arteriolar constriction which is manifest clinically as hypertension.

The view that a "renal factor" is the cause appears to be less popular as the evidence for it grows more complex (Goldring and Chasis, 1944, Smith, H. W., 1943). Although an obscure metabolic fault in the kidneys may eventually be incriminated, it is doubtful that renal ischemia as such is really responsible for the genesis of hypertension, even after consideration of such direct experimental approaches in man as the work of Dexter and Haynes (1944) and of Quinby and others (1945), dealt with in a previous section. The former workers concluded that the renin-pressor mechanism may be involved only initially in the development of hypertension.

It is doubtful whether a state of ischemia exists early in patients with hypertensive vascular disease sufficient to abolish the functional capacity of an enzymatic oxidative system in the kidneys. The decrease in renal blood flow and the elevation of filtration fraction occur earliest in the disease and appear to precede a decrease in the functional capacity of the renal tubules (Goldring and Chasis, 1944, Bradley, 1944).

In a study of the changes in hypertension and in renal function following unilateral nephrectomy, Friedman and others (1942) found that in none of their cases was there a complete return of the blood pressure to normal despite the fact that in 3 patients there was no "ischemia" of the remaining kidney. They concluded that renal ischemia may be a concomitant but not necessarily a causative factor in the pathogenesis of human hypertension.

According to Gubner and others (1946), in a review of the etiology of hypertension, there is no evidence that the renal pressor system plays a part in the initial stages of hypertensive vascular disease. They stated that the basal blood pressure, which may largely be determined by the humoral renal pressor mechanism, is normal in the earlier stages of hypertension. The humoral component may be important in the later stages when organic lesions in the renal (and other) arteries develop. Their suggestion is that neurogenic (vasomotor) components are responsible for the elevation of the blood pressure in the earlier stages of hypertensive vascular disease, attributed largely to psychosomatic influences.

In discussing the etiology of hypertensive vascular disease in a recent book, Herndon (1946) expressed the opinion that the mechanism is of humoral origin, since the process is reversible and denervation does not abolish it. It can arise from disease of the kidney, but this is not the general rule. The increased vascular resistance is not due primarily to organic changes in the vessel walls. The renal origin of hypertension is unproved.

From studies on dogs over a period of years, Grollman (1946) reported that chronic hypertension is not the result of liberation of a pressor substance by an ischemic or otherwise injured kidney, since removal of the constricted kidney fails to abolish it and the blood pressure is maintained even in the absence of all renal tissue. He stated that in experimental hypertension there is an acute rise probably due to tissue necrosis induced by "renal ischemia" but that the permanent rise which constitutes chronic hypertension requires weeks for its appearance and does not need the presence of renal tissue. To explain these findings, Grollman assumed that the kidney normally has a humoral function, interference in which by nephrectomy, constriction, ischemia or toxic agents results in a deficiency which is responsible for the observed rise in blood pressure.

The work of Selye (1946) already referred to shows that the nephrosclerosis and cardiovascular damage caused by anterior pituitary preparations and desoxycorticosterone is apparently not due to a direct action on the kidney and the cardiovascular system but is probably

mediated by the adrenal cortex, through the secretion of desoxycorticosterone-like compounds

The Role of the Adrenal Glands—The possible importance of the adrenal cortex in experimental "renal" hypertension (Goldblatt and others) was dealt with in a previous section. The possibility that adrenal ischemia may cause arterial hypertension has more recently been investigated by Victor (1945). In 6 dogs the application of ligatures around the vessels entering the left adrenal gland caused the systolic blood pressure to rise promptly from an average of 125 mm of mercury to 225 mm or more within two weeks. This hypertension was sustained in all the dogs for seven months (up to March 1946), comparable with the hypertension produced by experimental "renal ischemia" with the Goldblatt method. These results have been confirmed by Ogden and others (1948). The question now arises whether some methods of producing renal ischemia, with the ensuing hypertension, may not sometimes interfere with the blood flow through the adrenal glands, thus initiating changes which correspond with those following purposeful ligation of the adrenal vessels.

Evidence suggests that the endocrine system, like the nervous system, is of great importance in the genesis of certain types of hypertension, though probably subsidiary to other causes initiating the condition. Patients with hypertension do not commonly show obvious signs of endocrine dysfunction, but in animals ablation and other experiments clearly demonstrate the importance of the endocrine system, especially the adrenal cortex. In these cases possible modes of action might be (1) that too much adrenocortical hormone is produced, (2) that too little of the hormone is broken down, or (3) that the end organ, e.g., blood vessels, is hypersensitive to stimulation by the hormone.

Normally under basal conditions the caliber of the peripheral arterioles is not known to be greatly modified by products of the endocrine glands except in the case of the adrenal cortex. The presence of an excess of adrenal cortex hormone, as of epinephrine, such as is found in the presence of tumors of the adrenal gland may result in hypertension of the "essential type," which is completely relieved by removal of the tumor.

It may be concluded that this gland, and its governing body, the hypophysis, is involved directly or indirectly in the mechanism which raises arterial pressure. Among others, the gland contains substances which have estrogenic, progestational, androgenic and sodium-conserving functions. It is interesting that estradiol, progesterone, testosterone and desoxycorticosterone will induce elevation of the blood pressure of normal rats to hypertensive levels. In hypercorticoadrenalism producing the adrenogenital syndrome and Cushing's disease the adrenal dysfunc-

tion may lead to the development of hypertension through the production of abnormal steroids, estrogens and androgens and a variety of abnormal steroids have been demonstrated in the urine of patients with this condition

Enlargement of the adrenal glands in hypertensive conditions in man seems well established and appears to involve both cortical and medullary hyperplasia. It has still to be definitely shown whether the adrenal changes produce alterations in the cardiovascular system or develop secondarily to the hypertensive state. Much evidence favors the former view.

Perera (1945) reported an unusual and instructive case. A patient with hypertension in whom hypoadrenalism subsequently developed had persistent elevation of the blood pressure while receiving desoxycorticosterone. Administration of salt alone resulted in a fall of blood pressure to within normal limits although water and electrolyte balance was maintained. Perera suggested that the adrenal cortex may be important for the development or maintenance of hypertension.

The lack of knowledge concerning the relation of physiologic and pathologic processes in the cortex to circulatory disorders does not justify the assumption that cortical lesions are nonfunctional and clinically asymptomatic. The adrenal cortex may act in the following ways: (1) by its control over salt and water metabolism and the regulation of body fluid and blood volume, (2) by maintaining the responsiveness of the cardiovascular system to pressor substances in the blood or to other hypertensive stimuli or (3) by storing substances, i.e., lipid, protein, ascorbic acid, which are useful in the protection of the medullary hormone epinephrine against inactivation and destruction.

Cortical overactivity in hypertensive disease has been suggested by certain experimental and clinical observations cited already and is further suggested by certain associated metabolic abnormalities.

A. It is fair to say that retention of sodium chloride and water represents a significant contribution of cortical function to the maintenance or increase of blood pressure, although most of the other endocrine glands are also concerned in this process. The association of hypertension with retention of salt and water in adrenal, thyroid and pituitary disorders as well as in obesity and in toxemias of pregnancy is reviewed by Goldzieher (1944).

It has recently been found by Grollman and other (1945) that the administration of diets low in sodium content decidedly reduced the blood pressure of rats with experimental renal hypertension. They demonstrated, moreover, that the life of the animal was actually prolonged. In 2 of 6 hypertensive human subjects on a low sodium diet the blood

pressure was reduced to normal, with moderate reduction in 3 others and no decline in 1

B Hyperglycemia and reduced sugar tolerance are common in patients with renal hypertension or hypertensive vascular disease, according to von Noorden and Neubauer. Overactivity of adrenal cortex causes increased gluconeogenesis and decreased utilization of carbohydrate. These facts suggest that diabetes and hypertension may be coordinated and caused by the same influences. The frequent association of the two conditions appears more than coincidental. Hypertension and diabetes occurred five times as frequently in persons with cortical adenomas as in the general group (9,000 autopsies), and both diseases were frequently present in association with such tumors (Russi, 1945)

C Hypercholesterolemia is demonstrable in at least 70 per cent of all cases of renal hypertension and hypertensive vascular disease, cholesterol metabolism and its abnormalities are closely related to the function of the adrenal cortex. The mechanism of sensitization of the walls of the blood vessels to hypertensin may possibly be related to the use by the adrenal cortex of blood lipids and especially of cholesterol

Mention must be made of the important and now well established work of Selye (1936, 1944 and 1946) in regard to the probable role of the adrenal cortex in certain "diseases of adaptation," including hypertension. One of the most prominent morphologic changes in the "alarm reaction" is enlargement of the adrenal cortex due to hypertrophy of the individual cells and discharge of their lipid granules. True hyperplasia is usually less marked. This change is considered a sign of increased endocrine activity and takes several hours to develop, it continues to some extent as the organism becomes adapted to prolonged exposure to the stimuli (which may be of various kinds, e g, cold, fever, forced exercise, drugs or toxic tissue extracts). It has long been suspected that hormones are important in adaptive processes. In the "general adaptation syndrome," which is the sum of the nonspecific, adaptive, pathologic and biochemical reactions, certain changes depend on the integrity of the hypophysis and the adrenal cortex

In the reaction to continuous stress and strain, the anterior pituitary gland is actively engaged in producing an increase of corticotrophic hormone but elaborates less growth, lactogenic and gonadotrophic hormones. It appears that even the normal production of basic cortical hormone (corticoid) of the adrenal is enormous (Vogt, 1943), but during the alarm reaction phase of the general adaptation syndrome there is increased production of this hormone, according to Selye. This excess is produced under influence of the corticotrophic hormone and causes a number of secondary changes, especially in lymphatic organs, carbohydrate and electrolyte metabolism, the kidneys and the cardio-

vascular system Since overdosage with desoxycorticosterone produces such changes (in animals) as hypertension, vascular lesions like polyarteritis nodosa, myocardial lesions and lesions of the joints and nephrosclerosis, the possibility has arisen that certain diseases of man might result from excessive production of endogenous "salt-active" adrenal cortex hormones Selye expressed the belief that there is much evidence in favor of this interpretation, these hormones produced in response to stress may have detrimental side effects due to their inherent toxicity

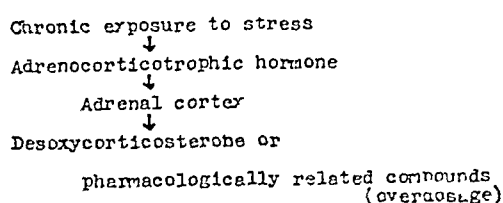
Recently Selye (1944) showed that anterior pituitary extracts can produce the same organic lesions as desoxycorticosterone, probably through the action of their corticotrophic factors releasing excess of desoxycorticosterone-like substances On the experimental evidence, this would appear to be the most probable hormonal mechanism in the body The final common hypophysoadrenal pathway could explain how the many different factors lead to the same end result

Many natural hormones, especially the trophic hormones of the anterior pituitary gland, appear to be proteins Proteins are certainly present in glandular extracts These proteins can act as antigens and lead to antibody formation (antihormones) This suggests that the phenomena such as periarteritis nodosa, arthritis and renal lesions produced in lower animals may be due to an antibody antigen reaction The same vascular reactions have been produced with the effector hormone desoxycorticosterone No antihormone has so far been produced for an effector hormone like epinephrine or estradiol The steroid hormones never form antihormones but may produce antibodies Zondek and Bromberg (1945) suggested that in certain circumstances patients may react to hormones produced by their own endocrine glands, various steroids including desoxycorticosterone were investigated by these workers Desoxycorticosterone administered to animals may perhaps combine with protein, and the resulting complex may act as an antigen, with sensitization of blood vessels then leading to vascular reactions There is evidence, however, that in man polyarteritis nodosa can result from exposure to a variety of nonspecific agents and in animals it is possible to reproduce this condition by such nonspecific damage as exposure to cold (Selye and Pentz, 1943)

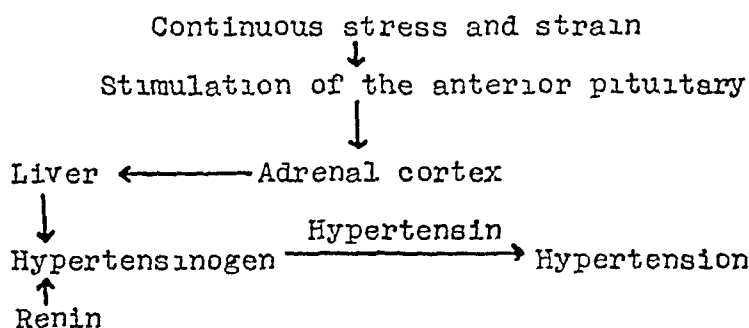
Experimental work has shown that the adrenal cortex is important in the production of hypertensinogen, probably stimulating its formation in the liver The presence of the adrenal glands or the administration of desoxycorticosterone is essential for a normal hypertensinogen level in rats The anterior pituitary gland and the adrenal cortex hormones may influence blood pressure directly through this mechanism, renal changes being independent of the high blood pressure or primary or secondary to it

The different types of adrenal cortex hormones may be produced in different proportions selectively stimulated by different adrenocorticotrophic principles. This is emphasized also by Albright (1942) and by Goldzieher (1944). Thus desoxycorticosterone or some related active steroid may be selectively elaborated under the influence of adrenocorticotrophic stimuli.

The following mechanism is suggested by Selve



The following schematic representation of the factors involved in the production of hypertension is suggested, based on the experimental work referred to in earlier sections of this work.



The concept that hyperfunction of the adrenal cortex may occur in the absence of demonstrable histologic changes is not disturbing since analogous endocrine paradoxes have been recognized for a long time and new ones have been described recently. For example, in cases of hyperthyroidism there is sometimes no evidence of hyperplasia when the gland is examined microscopically. Diabetes mellitus furnishes another example; few histopathologists would be willing to gage the severity of the disease by looking at the islets of Langerhans. The view has to be accepted that with the present relatively crude histologic technic the microscopic appearance of an endocrine structure may be an erroneous criterion of its secretory activity. The reverse problem also occurs. Thus, in recent literature there are two reports which indicate that functional adrenocortical insufficiency may occur in association with hyperplasia of the adrenal cortex (Wilkins and others, 1940, Dijkhuizen and Behr, 1939). In some cases the explanation may be that there is replacement of the interrenal tissue, notably the zona fasciculata, in which, according to Bennett's histochemical studies in the cat (1939), the cortical hormone is localized.

The Hypothalamic-Pituitary Mechanism—Increasing attention is being paid to the psychosomatic factor in diseases peculiar to civilized man. Environmental influences such as the "alarming stimuli" (Selye), as well as heredity, play an unquestionable role in the genesis of hypertension. The emotional make-up of a person and the stresses imposed on him are believed to play a part in many cases of hypertension. The nervous element in patients with hypertensive vascular disease has long impressed clinicians, though psychologic disorders and the physiologic disorder hypertension may represent reflections of a basic failure foreshadowed early in life.

Recent studies indicate that the hormones of the adrenal cortex play a significant role when the organism encounters or is subjected to situations of stress. Hoagland and others (1946) have demonstrated that the stress of certain psychomotor activity ("pursuitmeter" operation under anoxic conditions) causes increased adrenal cortex secretion. Organic disease of the central nervous system in man and experimental interference with the nervous system in animals can produce elevated blood pressure (Dock and others 1942).

The hypothalamus must be considered in the pathogenesis of hypertension. Its crowded "centers" synthesize and supervise numerous functions. It regulates the production of hormones of the anterior pituitary gland, through whose trophic influence it controls other endocrine glands. The hypothalamic-pituitary unit may lead to atrophy or hyperplasia of these glands or to formation of adenoma in them, however, such changes are not necessarily present, and alteration of hormone production may develop without such anatomic glandular changes.

Disorders of hypothalamic origin, metabolic, endocrine and cardiovascular, arise from the numerous afferent stimuli which the hypothalamic instrument receives in maintaining the internal milieu against environmental odds and mental (emotional) influences. The adrenal cortex "hormone" elevates the blood pressure, and desoxycorticosterone in large doses may produce arterial hypertension. This hormone is probably one of the agents by which hypertension of hypothalamic-pituitary origin is produced. The foregoing views are based on the statements on functional pathology by Lichtwitz (1942).

The Basis of the Treatment of Hypertension—The unsatisfactory nature of present knowledge of the cause and treatment of hypertension is shown by the number of drugs and methods used in its control. Various surgical, dietary and pharmaceutic measures have at one time or another offered promise.

A Sympathectomy. The chromaffin cells of the adrenal medulla have a rich nerve supply from the splanchnic nerves (sympathoadrenal system), but the effect of sympathetic denervation on the adrenal cortex is unknown.

The mechanism by which high blood pressure is lowered in man by double lumbodorsal sympathectomy (Smithwick) is not completely understood. One suggestion has been that the lowering may be due to a favorable effect on factors which combine to reduce or alter renal blood flow, which in turn results in impairment of function and in destruction of renal tissue, however, this is probably not correct as it is generally agreed that denervation of the kidneys in man and animals causes no consistent effect on the excretory function or on blood flow. Another view is that there may be an extrarenal effect such as vascular relaxation, either arterial or venous or both, or that the decrease is due in part to inhibition of or interference with adrenal secretion (White and Smithwick, 1942). The recent discovery of Victor (1945) mentioned earlier, supported by the work of Ogden and others, that partial ligation of the adrenal vessels on one side causes sustained hypertension in dogs, might provide support for this last suggestion.

Berwald and Devine (1944) stated that the rationale for sympathectomy is based on (a) relaxation of blood vessels of the lower limbs and the splanchnic area, (b) increased blood supply to the kidney and (c) decrease in the amount of epinephrine secreted through fear, excitement or other vasomotor stimuli.

The operation of splanchnic section denervates the adrenals as well as the kidneys, so that the adrenal denervation may be responsible for the relief (symptomatic) obtained by patients with hypertension. Vogt showed (1944), as mentioned in a previous section, that repeated injections of epinephrine in animals cause an increased output of cortical hormone and an increase in the weight of the adrenals associated with storage of lipin.

An interesting and important physiologic observation is that the patients on whom a "successful" operation was performed show similar reactions to posture and to cold after the sympathectomy, but with lower levels of blood pressure. This neurosurgical approach to the treatment of hypertension is unsatisfactory because it does not take cognizance of the primary causal factors of the disease. It merely destroys one of the several physiologic mechanisms which maintain vascular tone.

Gold (1945) expressed the belief that while sympathectomy produces impressive initial lowering of the blood pressure in hypertension the number of successful "cures" by this method will be small. He regarded the protracted inactivity and the revised attitude and habits of the patient who has subjected himself to this serious operation as the cause of the longer lasting moderate reduction of the blood pressure.

The symptomatic improvement which occurs frequently after the Smithwick operation and after thiocyanate therapy, even without lowering of the blood pressure, has still to be explained.

B Thiocyanate Therapy Apart from the surgical treatment for hypertension, administration of potassium thiocyanate is the only other practical method of reducing the blood pressure. The mode of action of this drug is not understood. It may act against a pressor substance. One study of interest (Healy, 1931) showed that the cut surface of the adrenal body revealed strong evidence of thiocyanate in the cortex when the potassium salt was given to rabbits, which suggests the possibility of accumulation of the drug in the adrenal glands.

C Nonspecific or Inflammatory Reactions Taylor and Page (1944) investigated the mechanism of the reduction of arterial pressure in hypertensive patients and animals following nonspecific and inflammatory reactions, and they showed that neither fever nor leukocytosis is the cause. They suggested that the reactions impair that function of the adrenal cortex which maintains vascular reactivity and elevated blood pressure and so produce a reduction of arterial pressure.

CONCLUSIONS

A comprehensive and critical survey of the literature dealing with arterial hypertension leads one to conclude that until further evidence becomes available it is best to regard hypertensive vascular disease as non-renal in origin. This point of view is accepted by Ellis (1942) and by other authorities, thus, Homer Smith and others (1943) have stated that so far as the genesis of this condition is concerned the kidney appears to be the victim rather than the culprit. This is confirmed by the conclusion reached by Page (1943, 1944) that there is little evidence that persistent reduction of blood flow and oxygen utilization occurs within the kidneys except when hypertension is of long duration and severe secondary vascular change has supervened.

An attempt has been made in the present study to show that the adrenal cortex plays a major role in arterial hypertension, and much experimental and clinical data have been submitted. While there is much evidence for this point of view, final proof must still be awaited.

G SUMMARY OF REPORTS INDICATING THE SIGNIFICANCE OF THE ADRENAL CORTEX IN ARTERIAL HYPERTENSION

The morphologic changes are given in table 1 and are described more fully in section C. The more significant experimental and clinical findings are given in the following paragraphs.

Bilateral adrenalectomy abolishes experimental renal hypertension, the hypertension can be produced if even a minute portion of the adrenal cortex is left or if the completely adrenalectomized animal is given cortical

extract (Goldblatt, 1937, Blalock and Levy, 1937, Page, 1938, Grollman, 1940, Dell'Oro, 1942)

The renin substrate hypertensinogen is a globulin formed in the liver and possibly in the adrenal cortex. It decreases and even disappears from the systemic blood of untreated adrenalectomized male dogs (Lewis and Goldblatt, 1942, Houssay and Dexter, 1942). Adequate doses of adrenal cortex hormone or of desoxycorticosterone cause a return of hypertensinogen to a normal level.

Bilateral adrenalectomy decreases the response to injections of renin (Page, 1939, Williams and others, 1939, Friedman and his associates, 1940, Remington and others, 1941, Swingle and Remington, 1944). It prevents the appearance of a substance like angiotonin in the blood when experimental hypertension is produced in the dog by injection of kaolin into the cerebral ventricles.

Adrenal cortex tissue or certain of its hormones (desoxycorticosterone or 17-hydroxy-11-dehydrocorticosterone) seem necessary for the existence

TABLE 2—*Reports on the Production of Hypertension with Adrenocortical and Other Hormones*

Effects in man—with desoxycorticosterone		
Cleghorn and others	1939	In Addison's disease
Ferrebee and others	1939	In Addison's disease
McGavack	1941	In Addison's disease
Perera and others	1944	In Addison's disease
Soffer and others	1940	In Addison's disease
Thorn and Firor	1940	In Addison's disease
Effects in animals—with 17-hydroxy-11-dehydrocorticosterone		
Kuhlman and others	1939	In dogs
Remington and others	1941	In adrenalectomized dogs
Rodbard and Freed	1942	In dogs
Swingle and others	1941	In normal and adrenalectomized dogs
Briskin and others	1943	In rats
Gaudino	1945	In hypertensive adrenalectomized rats
Grollman and others	1940	In rats
Knowlton and others	1946	In rats with cytotoxic serum nephritis
Leathem and Drill	1944	In rats
Selye	1946	In rats
Effects in animals—with 17-hydroxy-11-dehydrocorticosterone		
Gaudino	1945	In hypertensive adrenalectomized rats
Effects in animals—with stilbestrol		
Grollman and others	1940	In rats
Hill	1946	In rats
Leathem and Drill	1943	In normal and hypophysectomized rats
Oster	1946	In castrated rats
Sapeika		In rats

of "renal" hypertension and for the maintenance of normal arterial pressure.

Hypophysectomy in rats with "renal" hypertension causes a fall of blood pressure, which is restored to the original level by administration of adrenocorticotrophic hormone.

Hypophysectomy or adrenalectomy in rats with "renal" hypertension causes a fall in the level of blood pressure, which may be partially restored by the administration of adrenal cortex extracts or desoxycorticosterone but not by the use of such steroids as progesterone, testosterone or estradiol (Page and others, 1946).

Ligation of vessels to an adrenal gland produced sustained hypertension in dogs comparable with that produced by the Goldblatt method (Victor, 1945, Ogden and others, 1948)

Successful reduction of the systolic and diastolic pressures for months was obtained in cases of hypertension by subtotal bilateral adrenalectomy (DeCourcy, 1934)

In cases of Cushing's syndrome due to adrenal carcinoma the raised blood pressure returned to normal after removal of the tumor (Silver, 1940)

A patient with hypertension in whom Addison's disease subsequently developed had a persistently elevated blood pressure while receiving desoxycorticosterone (Perera, 1945)

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ORGANISMS RESISTANT TO PENICILLIN OBTAINED FROM PATIENTS

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IT IS GENERALLY supposed that bacteria which are sensitive to the action of penicillin seldom acquire resistance to this antibiotic as a result of the treatment of human infections. In most cases of infection amenable to penicillin therapy a prompt clinical response is obtained and administration is discontinued. Generally, there is little opportunity for resistant strains to develop in such cases as the period of treatment is usually of relatively short duration.

The appearance of resistant organisms while the patient was under treatment with penicillin has been reported¹. In most of the cases the

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1 Spink, W. W., Ferris, V., and Vivino, J. J. Antibacterial Effect of Whole Blood upon Strains of Staphylococci Sensitive and Resistant to Penicillin, *Proc. Soc. Exper. Biol. & Med.* **55**: 210 (April) 1944. Gallardo, E. Sensitivity of Bacteria from Infected Wound to Penicillin. II. Results in One Hundred and Twelve Cases, *War Med.* **7**: 100 (Feb.) 1945. North, E. A., and Christie, R. Observations on the Sensitivity of Staphylococci to Penicillin, *M. J. Australia* **2**: 44 (July 14) 1945. Buchman, J., and Blair, J. E. Penicillin in the Treatment of Chronic Osteomyelitis, *Arch. Surg.* **51**: 81 (Sept.) 1945. Report on the Use of Penicillin in the Treatment of Staphylococcal Infections, with Special Reference to Acute and Chronic Osteomyelitis and Several Collateral Studies, *Bull. Hosp. Joint Dis.* **6**: 114 (Oct.) 1945. Todd, E. W., Turner, G. S., and Drew, L. G. W. "Fastness" of Staphylococci, Haemolytic Streptococci, and Pneumococci to Penicillin, *Brit. M. J.* **2**: 603 (Nov. 3) 1945. North, E. A., and Christie, R. Acquired Resistance of Staphylococci to the Action of Penicillin, *M. J. Australia* **1**: 176 (Feb. 9) 1946. Blair, J. E., Carr, M., and Buchman, J. The Action of Penicillin on Staphylococci, *J. Immunol.* **52**: 281 (March) 1946. Harley, H. R. S., Baty, J. A., and Bowie, J. H. The Pathogenicity of Penicillin-Insensitive Infection, *Brit. M. J.* **2**: 639 (April 27) 1946. Franks, A. G. Successful Combined Treatment of Penicillin-Resistant Gonorrhea, *Am. J. M. Sc.* **211**: 553 (May) 1946. Mascall, W. N. Penicillin for Gonorrhea in the Female, *Lancet* **2**: 712 (Nov. 16) 1946. Pulaski, E. J. Streptomycin Therapy of Penicillin-Resistant

sensitivities of the organisms had not been determined before treatment was started so that the strains may have been naturally resistant. In other cases the bacteria were isolated from open wounds and thus were exposed to contamination from outside sources, so that it is impossible to determine whether the resistant strains were derived from the organisms originally present or whether they came from the outside.

In some infections, such as staphylococcic bacteremia or endocarditis caused by *Streptococcus viridans*, even though recovery may take place slowly, the antibiotic usually clears the blood stream rapidly. After penicillin treatment has been started, bacteria usually cannot be obtained by culturing the blood, and consequently they are not suitable for subsequent determinations of sensitivity.

Several investigators² have reported the development of resistant strains of *Str. viridans* in patients during treatment with penicillin for endocarditis. In the course of studying 75 patients with bacteremia or endocarditis, we encountered 14 patients on whom positive blood cultures were obtained after penicillin therapy had been started. In each instance the organism was identical, so far as could be determined, with the organism present in the blood before the start of treatment. It is the purpose of the present paper to discuss the circumstances in which this phenomenon occurred and to compare the penicillin sensitivities of the organisms at various stages during the course of treatment of the disease.

Our experience with regard to the penicillin sensitivity of pneumococci and beta hemolytic streptococci has been similar to that of others. Almost all the strains tested were extremely sensitive to penicillin. In only one publication³ has there been reported a highly resistant strain of a beta hemolytic streptococcus. We have encountered three strains of beta hemolytic streptococci and one strain of pneumococcus which were relatively resistant to penicillin. The details of these cases are being reported herewith.

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TABLE 1—Data on the Bacteria Developing Resistance During Penicillin Therapy

Patient	Diagnosis	Organism	Original Sensitivity to Penicillin (Units/Cc)	Day of Recurrence of Positive Blood Culture	Sensitivity to Penicillin at Time of Recurrence (Units/Cc)	Fold Increase	Dose At Time of Change in Sensitivity (Units) *	Blood Concentrations of Penicillin (Units/Cc Serum)			Result
								1 Hour after Injection	2 Hours after Injection	3 Hours after Injection	
1	Bacteremia	Staphylococcus albus hemolytic, coagulase —	0 022	3 5 12	0 044 0 089 1 45 0 72	2 4 32	75,000 every 2 hr orally 75,000 every 2 hr orally 50,000 every 2 hr None Streptomycin†	0 039	0	0	Recovered with the use of streptomycin
2	Bacteremia	Staphylococcus aureus, hemolytic, coagulase +	0 195	7	1 45	8	100,000 every 2 hr 500,000 every 2 hr †	—	—	—	Infection controlled, died of debility
3	Bacteremia	Hemolytic streptococcus	0 089	3 4	20 00 20 00	512 512	1,000,000 every 2 hr 1,000,000 every 2 hr † Caronamidet	10 00	5 00	—	Recovered
4	Endocarditis	Staph albus, nonhemolytic, coagulase —	0 089	1 2	0 72 1 42	8 16	100,000 every 2 hr 100 000 every 2 hr 1,000,000 every 2 hr †	1 25	0 312	—	Died of overwhelming infection
5	Endocarditis, arthritis	Staph aureus hemolytic, coagulase +	0 022	7	0 89	4	25,000 every 3 hr 50 000 intra articularly 50,000 every 3 hr †	0 312 (0 625 in joint fluid)	0 156	0 039	Recovered
6	Endocarditis	Staph aureus, hemolytic, coagulase —	0 312‡	Daily from 7 to 13	20 00	64	1,000,000 every 2 hr 1 000 000 every 2 hr † Caronamidet 2,000,000 every 2 hr † Caronamidet	5 00 10 00	2 5 5 00	—	Died of overwhelming infection
7	Endocarditis	Staph aureus, nonhemolytic, coagulase +	0 044	14 20 27	0 089 0 178 0 356	2 4 8	15,000 every 2 hr 50,000 every 2 hr 75 000 every 2 hr 1,000,000 every 24 hr †	0 078 0 625 1 25	0 039 0 156 0 312	—	Recovered
8	Endocarditis	Staph aureus, nonhemolytic, coagulase —	0 078	20	0 625	8	200 000 every 2 hr 2,000,000 every 2 hr †	—	—	—	Recovered

Patient		Diagnosis	Organism	Original Sensitivity (Units/Cc)	Day of Recurrence of Positive Blood Culture	Sensitivity of Organism to Penicillin at Time of Recurrence (Units/Cc)	Fold Increase	Dose At Time of Change in Sensitivity (Units) *	Blood Concentrations of Penicillin (Units/Cc Serum)			Result
									1 Hour after Injection	2 Hours after Injection	3 Hours after Injection	
Symptoms of Active Infection	9	Endocarditis	Str viridans	0 0007	3 21 29 31	0 011 0 044 0 179 1 43	16 64 256 2048	100,000 every 2 hr orally 25,000 every 2 hr 30,000 every 2 hr 300 000 cont every 24 hr 1,000,000 cont every 24 hr †	0 039	0	Recovered	
									0 312	0 039		
									0 312	0 039		
									range, 0 312 to 1 25			
10	Endocarditis	Str viridans	0 039	8	0 625	16	30,000 every 2 hr 60,000 every 2 hr †	0 625	0 078	Recovered		
Asymptomatic	11	Bacteremia	Staph albus, hemolytic, coagulase —	0 089	16	0 178	2	75,000 every 2 hr	0 625	0 312	Recovered	
	12	Bacteremia	Staph aureus, hemolytic, coagulase +	0 195	6	0 780	4	1,000,000 every 2 hr	—		Recovered	
	13	Endocarditis	Staph aureus, hemolytic, coagulase +	0 089	2	0 178	2	75,000 every 2 hr	0 312 0 625	0 156 0 312	Recovered	
	14	Endocarditis	Str viridans	0 019	26	0 039	2	50,000 every 3 hr	0 625	0 312	0 156 Recovered	

*All patients received penicillin intramuscularly unless otherwise indicated

†Final dose

‡Caronamide was given in doses of 4 Gm every four hours

§Recurrence of organism in blood culture during first three days of therapy without change in sensitivity

"ACQUIRED" RESISTANCE

Of 75 patients with endocarditis and bacteremia treated with penicillin, 14 had one or more recurrences of positive blood cultures during therapy. In each instance the causative organism was found to be more resistant than at the start. Invariably, the original sensitivity was based on determinations⁴ on the organism isolated from at least two different cultures taken at different times. The pertinent data from the case histories of these patients are shown in table 1. In the first 10 patients the recurrence of bacteremia was accompanied with symptoms of active infection. There were 2 patients with staphylococcic bacteremia, 1 with hemolytic streptococcic bacteremia, 5 with staphylococcic endocarditis and 2 with endocarditis caused by *Str. viridans*. In all but 1 of the patients bacteremia disappeared, only to recur sometime from the third to the thirty-first day of treatment with penicillin. In the patient mentioned, bacteremia persisted for the two days that penicillin was administered before his death.

The increase in resistance ranged from fourfold to two thousand and forty-eight fold. It can be seen that there is no correlation between the initial sensitivity and the height and rapidity of the development of resistance. Six strains exhibited increases on one occasion, one on two occasions, one on three occasions and two on four occasions. The blood penicillin concentrations were determined in 8 of these patients after the appearance of organisms with increased resistance which developed while the patients were still on the same dosage schedule. If one considers penicillin therapy to be adequate when the blood concentrations are always greater than the *in vitro* sensitivity of the organism, then there was no correlation between the development of resistance and the adequacy of therapy, since in 4 of the patients the concentrations in the blood were always bactericidal. On the other hand, if, as some investigators believe, penicillin blood concentrations four to eight times the *in vitro* sensitivity of the causative organisms are necessary in cases of endocarditis, none of these patients can be considered as having received adequate treatment. The dose was increased in all cases, and recovery followed in 6. One patient died of debility after the infection was controlled, 2 died of overwhelming infection and another was ultimately cured with streptomycin.

In the other group of 4 patients, 1 each with staphylococcic endocarditis and endocarditis caused by *Str. viridans* and 2 with staphylococcic bacteremia, the appearance of positive bacteriologic signs after treatment was begun was not accompanied with symptoms of active infection. In 1 patient bacteremia persisted through the second day of treatment, while

4 The determinations were made by the serial dilution method

in the remaining patients bacteremia disappeared after penicillin was started, only to recur daily from the sixth to the twenty-sixth day of therapy. Three of the strains demonstrated a twofold increase in resistance and the fourth a fourfold increase. Adequate blood concentrations of penicillin were found in the 3 patients in whom they were determined. The doses of penicillin were continued and all the patients recovered.

One of the problems was to determine the significance of the increased resistance of the infective bacteria in these patients. In an occasional organism as much as an eightfold increase in sensitivity to penicillin has been observed to occur spontaneously or as a result of the inaccuracy of the method of assay. It is believed, however, that the increases in resistance to penicillin observed in the first 10 patients in table 1 represented a true change in penicillin sensitivity, since symptoms of an ac-

TABLE 2—*Data on Bacteria Resistant to Penicillin*

Patient	Diagnosis	Organism	Source of Culture	Sensitivity (Units/cc)	Dose	Result
1	Scarlet fever	Hemolytic streptococcus	Throat	20	300,000 units in oil and beeswax once a day for 5 days	Recovered, penicillin ineffective
2	Pharyngitis	Hemolytic streptococcus	Throat	20	100,000 units every 4 hr for 5 days	Recovered, penicillin ineffective
3	Erysipelas	Hemolytic streptococcus	Blood, nose, throat	>200	600 000 units in oil and beeswax for 2 doses 1,000,000 every 2 hr for 1 dose	Died
4	Pneumonia	Pneumococcus, type I	Sputum	>20	600 000 units in oil and beeswax twice a day for 10 days	Recovered with the use of sulfadiazene

tive infection were present at the same time. On the basis of the results of the determinations of the concentrations of penicillin in the blood, it would appear that therapy given to these patients was inadequate. Furthermore, we have not noted a spontaneous change in sensitivity greater than fourfold with repeated sensitivity determinations on twenty-seven organisms transferred from two to fifty times in artificial mediums. In addition, in only one of several hundred determinations have we found a difference greater than fourfold when multiple determinations of sensitivity were performed on the same organism isolated at different times from patients not receiving specific therapy.

The significance of the increased resistance in the last 4 patients is unknown. Whether it represented a laboratory error or an actual change in sensitivity without clinical significance is a matter of speculation.

"NATURAL" RESISTANCE

Four strains of bacteria were isolated from patients before treatment was started that were apparently relatively insensitive to penicillin (table 2). Two of the strains of beta hemolytic streptococci were isolated from cultures of the throats of 2 patients with scarlet fever and septic sore throat, respectively. In neither instance was the sensitivity of the streptococcus determined before therapy was started. The patient with scarlet fever was treated with daily injections of 300,000 units of penicillin in oil and wax, and the other patient received 100,000 units of penicillin orally every four hours. After three days of therapy there was no clinical or bacteriologic improvement in either patient, and cultures of the throats revealed organisms resistant to 10 and sensitive to 20 units of penicillin per cubic centimeter of medium. Administration of penicillin was continued for two additional days, and the course was that usually seen in patients treated symptomatically.

The third patient was admitted to the hospital with symptoms and signs of acute sinusitis and pneumonia. After cultures of material from the throat and blood cultures were taken, she was placed on a regimen of 600,000 units of penicillin in oil and wax every twelve hours. The following day erysipelas of the face developed. In the meantime, a beta hemolytic streptococcus was isolated from the throat and blood cultures. Both strains were found to be resistant to 20 units of penicillin per cubic centimeter of medium. Within the period that it took to determine the sensitivities the patient died. At autopsy there were no abnormalities except for the erysipelas and evidence of toxic changes in the various organs incident to the infection.

The fourth patient was admitted to the hospital with symptoms and signs of pneumonia of the upper lobe of the right lung. A type I pneumococcus was isolated from his sputum. After two days of therapy consisting of 600,000 units of penicillin in oil and wax every twelve hours, during which time there was no improvement, the sensitivity of the organism was determined, and it was found to be resistant to 200 units of penicillin per cubic centimeter of medium. The patient's condition was later diagnosed as pulmonary tuberculosis, so that the significance of the pneumococcus is undetermined. In any event, the epidemiologic significance of this strain is obvious.

COMMENT

Three theories of the development of resistance have been proposed: adaptation, mutation and selection.⁵ The first two theories suppose that

5 Demerec, M. Production of *Staphylococcus* Strains Resistant to Various Concentrations of Penicillin, *Proc Nat Acad Sc* 31: 161 (Jan) 1945.

all members of the bacterial population were originally sensitive and that as a result of exposure to penicillin there occurs some change in their physical-chemical state or in their metabolic requirements. The third theory proposes that in any bacterial population the sensitivity of the members varies and that resistant members or mutants are present originally. On exposure to penicillin the sensitive members are killed, while the resistant members survive (survival of the fittest). The resistant members apparently may not influence the original determination of sensitivity because of their limited numbers. Under the conditions of the test, the organisms do not proliferate sufficiently to influence the result.

Regardless of the mechanism involved, subbactericidal concentrations of penicillin apparently are a prerequisite for the development of resistance. Inadequate penicillin therapy may be the result of insufficient amounts of the antibiotic or of unusually rapid excretion by the patient. In certain infections such as endocarditis and osteomyelitis, in which, because of the nature of the lesions or the avascularity of the tissue, the penetration of penicillin into the tissues is poor, there is greater opportunity for resistance to develop. Furthermore, certain bacteria such as staphylococci and *Str. viridans* develop resistance with great facility. In the 10 patients in whom the causative organism developed increased resistance to penicillin one or more of these factors were probably operative.

It is obvious from the data in table 1 that the initial sensitivity to penicillin is not a factor in the development of the resistance, although it has been suggested that strains relatively insensitive originally develop resistance with greater ease. The data indicate that there was great variation in the speed and height of the development of resistance, but we were unable to determine any factors which governed this phenomenon.

As a result of these and other studies, we have found that the penicillin sensitivity may serve as an aid in the identification of bacteria. We have noted many instances in which organisms isolated at different times were alike in all their cultural characteristics except the penicillin sensitivity, and ultimately it was concluded that actually there were different strains.

Penicillin-sensitive bacteria have developed resistance in the test tube on exposure to increasing sublethal concentrations of penicillin and during the treatment of infections in human beings with inadequate doses. In addition, naturally resistant strains have been observed among the bacteria generally susceptible to penicillin. These laboratory and clinical observations confirm the necessity for adequate bacteriologic study and follow-up on all patients receiving antibiotic therapy whenever possible. In cases of endocarditis and infections caused by staphylococci and certain strains of *Str. viridans* the sensitivity to penicillin should be determined and treatment arranged accordingly. Furthermore, in order to

insure adequate concentrations in the tissues and also to compensate for errors in the method of determination of sensitivity, blood penicillin concentrations four to eight times the *in vitro* sensitivity should be maintained. These precautions will help to minimize the development of resistant organisms during therapy with penicillin.

SUMMARY AND CONCLUSIONS

1 Fourteen of 75 patients with infections of the blood stream had a recurrence of positive blood cultures during penicillin therapy. All the organisms demonstrated an increase in resistance to penicillin. In 10 patients the increase in resistance was fourfold or greater and was accompanied with symptoms of active infection. The increased resistance of the organisms in 4 patients was fourfold or less and not accompanied with symptoms of infection.

2 Three strains of beta hemolytic streptococci and one strain of a type I pneumococcus were isolated which were resistant to penicillin before therapy was begun.

3 In cases of bacteremic or other serious infections caused by staphylococci or alpha and gamma streptococci the sensitivity of the organism to penicillin should be determined before treatment is instituted and careful bacteriologic follow-up should be maintained.

4 In cases of infections which are usually amenable to penicillin therapy the sensitivity of the causative organism should be determined when there is no response to treatment.

Book Review

Sexual Behavior in the Human Male By Alfred C Kinsey, Wardell B Pomeroy and Clyde E Martin Price, \$6 50 Pp 804, Philadelphia W B Saunders Company, 1948

This study is a monumental contribution to our knowledge of the sexual behavior of the human male It is accurately described by its authors as "a fact-finding survey to discover what people do sexually, and what factors account for differences in sexual behavior among individuals, and among various segments of the population" The data have all been obtained in personal interviews, each of approximately two hours' duration To date, 12,000 persons have been studied, of these, 6,300 are males and 5,300 white males on which the present volume is based The conclusions are of far reaching import and deserve the attention not only of medical men but of all of those who are seriously interested in our American social scene

Certain criticisms, for the most part pointed out frankly by the authors, are legitimate but scarcely detract from the value of the work For example, it is a study not of all kinds of men but only of white men in the United States and in the twentieth century It is, furthermore, rather heavily weighted with an urban and academic selection, it samples too few men over 50 years of age, too few factory workers and manual laborers and too few children, and it reserves for future reports all consideration of the highly interesting Negro male Further, it is, of course, a study only of what men *say* they do Despite scrupulous and ingenious cross checks and guards against falsification, it is necessarily colored somewhat by the errors of memory, by the fact that some men are given to boasting and others to reticence and by unconscious tendencies in the individual to say about himself what he considers to be "normal" or expected Unfortunately, no study of large numbers can in any sense measure the subtle psychologic factors underlying sexual behavior or the emotional tones accompanying it Finally, as others have pointed out, this report is a record of the testimony only of those men who chose to testify and misses those who for one reason or another refused

With all these reservations, it must be admitted that the work is in general a fair documentation of the sexual life of the modern white American male The interview method, with all its limitations, is indisputably far superior to the almost worthless questionnaire method And for extensive coverage, wealth of detail and meticulous and critical statistical analysis, the study is incomparable in medical and sociologic literature

To medical readers, and especially to psychiatrists, many of the revelations in the book come as no surprise For example, physicians have long known or suspected the early development of erotic interests and overt sexual behavior and the high incidence of masturbation (92 per cent among the male population), of isolated (but not habitual) homosexual experiences (37 per cent) and of premarital (67 to 98 per cent) and extramarital (about 50 per cent) heterosexual

indulgence. However, it is arresting to learn of the differences in sexual behavior between the lower and higher educational and social strata and the rather widely divergent customs and taboos in the two groups. These differences are so great that it is no longer legitimate to speak of the sexual habits of the average man without specifying which average is meant. Of great interest also is the doubt, expressed by the authors in a long and closely reasoned passage, as to the existence of the commonly accepted idea of "sublimation."

In a review of this sort no extended critique can be given. But for every serious physician this landmark in sociologic fact finding is not only an indispensable source of information on a topic too long left to conjecture but also an absorbingly interesting one.

PERIPHERAL NEURITIS IN PERIARTERITIS NODOSA

A Clinicopathologic Study

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NEURITIS in periarteritis nodosa occurs more frequently than is commonly supposed. In the original description of the disease by Kussmaul and Maier¹ in 1866, the neurologic manifestations were prominently portrayed. It is somewhat surprising, then, that the clinical and pathologic aspects of involvement of peripheral nerves in periarteritis nodosa have received so little attention. Clinically, the role of peripheral neuritis has been difficult to assess because of the confusion which has arisen concerning the interpretation of purely subjective symptoms in a disease also characterized by arthritis and myositis. Pathologically, the chief drawbacks to a more complete understanding have been the infrequency of removal of peripheral nerves at autopsy and the difficulty in drawing conclusions from the study of only a small portion of a nerve.

REPORTS IN THE LITERATURE

The reports of peripheral neuritis in periarteritis nodosa are, for the most part, widely scattered in the literature and total a relatively small number of cases. Especially lacking are studies which include histologic examination of the involved nerves in a significant number of cases. The largest single series of this type was reported by Marcus² in 1933. He listed 7 cases in which microscopic examination was carried out on

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Abridgment of thesis submitted by Dr. Lovshin to the faculty of the Graduate School of the University of Minnesota in partial fulfillment of the requirements for the degree of Master of Science in Medicine.

1 Kussmaul, A., and Maier, R. Ueber eine bisher nicht beschriebene eigenthumliche Arterienerkrankung (Periarteritis nodosa), die mit Morbus Brightii und rapid fortschreitender allgemeiner Muskellahmung einhergeht, *Deutsches Arch f klin Med* 1:484-518, 1865-1866.

2 Marcus, H. Polyneuritis perivasculitica, *Acta psychiat et neurol* 8:297-329, 1933.

peripheral nerves obtained either by biopsy or at necropsy, several of the cases were atypical. It is significant that since the first American report of periarteritis nodosa by Longcope³ in 1908 only three publications on the peripheral neurologic features of this disease have appeared in the American literature. Kernohan and Woltman,⁴ Boyd⁵ and Wechsler and Bender⁶ wrote on the clinical aspects, while only the first-named authors reported the histologic changes observed in the involved nerves.

Attempts by various reviewers to establish the incidence of peripheral neuritis in periarteritis nodosa revealed widely different figures. The percentage of neuritis as based on clinical criteria varies from 12 to 50 per cent in different series. Boyd, in 1940, in an admirable review of the 395 cases reported in the world literature found that 129 (33 per cent) showed "neuromyositic symptoms exclusive of arthralgias."

The incidence of involvement of peripheral nerves, as evidenced by microscopic studies, is even more difficult to determine. The obvious reason is that specimens of peripheral nerves are frequently not obtained at autopsy. Another serious difficulty is that in most reports it is not specifically stated whether the nutrient vessels alone are involved or whether there is accompanying degeneration of the nerve fibers. Gruber,⁷ in 1926, summarized the 115 cases of periarteritis nodosa which had been reported up to that time. In 108 of these, sufficiently complete post-mortem studies had been made to warrant a listing of the organs affected. Twenty (19 per cent) showed involvement of the peripheral nerves. Arkin,⁸ in 1930, reported involvement of nerves in 20 per cent of cases.

Because of the scatter and infrequency of the earlier reported cases, there was little or no attempt to define the symptom complex associated with involvement of the peripheral nerves. Most authors reported instances of generalized neuritis of the extremities, though Ferrari,⁹ in

3 Longcope, W. T. Periarteritis Nodosa, with Report of a Case with Autopsy, *Bull. Ayer Clin. Lab., Pennsylvania Hosp.* 5:1-31 (Dec.) 1908.

4 Kernohan, J. W., and Woltman, H. W. Periarteritis Nodosa. A Clinico-pathologic Study with Special Reference to the Nervous System, *Arch. Neurol. & Psychiat.* 39:655-686 (April) 1938.

5 Boyd, L. J. Periarteritis Nodosa. Neuromyositic Manifestations, *New York M. Coll. & Flower Hosp. Bull.* 3:272-279 (Dec.) 1940.

6 Wechsler, I. S., and Bender, M. B. The Neurological Manifestations of Periarteritis Nodosa, *J. Mt. Sinai Hosp.* 8:1071-1078 (Jan.-Feb.) 1942.

7 Gruber, G. B. Kasuistik und Kritik der Periarteritis nodosa, *Zentralbl. f. Herz- u. Gefasskr.* 18:185-198 (May) 1926.

8 Arkin, A. A Clinical and Pathological Study of Periarteritis Nodosa. A Report of Five Cases, One Histologically Healed, *Am. J. Path.* 6:401-426 (July) 1930.

9 Ferrari, E. Ueber Polyarteritis acuta nodosa (sogenannte Periarteritis nodosa), und ihre Beziehungen zur Polymyositis und Polyneuritis acuta, *Beitr. z. path. Anat. u. z. allg. Path.* 34:350-386, 1903.

1903, observed medial paralysis during the course of this disease. More recently, it was stated that the most suggestive feature of the peripheral neuritis is its variable behavior. It may begin abruptly or develop slowly, affecting a single nerve or many. When multiple neuritis is present, it tends to be asymmetric and the nerves are affected individually and at different times—the so-called mononeuritis multiplex. The neuritis may regress, recur or remain as a sequela. Regression of the peripheral neuritis during the course of the disease is fairly common. Upper and lower extremities are involved with equal frequency, almost invariably the neuritis is more pronounced peripherally. The most frequent signs and symptoms are pain, paresthesias, anesthasias, tenderness of the nerve trunks and muscles, paralysis, loss of reflexes and atrophies. The motor paralysis presents typical lower motor neuron manifestations in the vast majority of cases.

A limited number of reports described the microscopic appearance of peripheral nerves affected by periarteritis nodosa. It is agreed that the nutrient arteries are frequently involved and that these arteries show the same changes seen in the vessels of other parts of the body. Most observers noted degenerative changes in the nerve fibers identical with those of simple wallerian degeneration. Depending on the degree of involvement and the stage of dissolution, the changes consist in swelling, beading and fragmentation of the myelin sheaths and axis-cylinders, increase of the number of cells in the sheath of Schwann, removal of debris by fat-ingesting macrophages and, finally, fibrous tissue replacement in the nerve bundles. Edema of the nerve trunks and thickening of the epineurium and perineurium are frequently described nonspecific changes. Kernohan and Woltman called attention to localized regions of infarction in the nerve bundles. No evidence of interstitial neuritis has been reported. The inflammatory changes occur only in and around the arterial wall. The connective tissue elements of the peripheral nerves are not directly involved. The neurologic lesion appears to be a simple degeneration.

The cause of the degeneration of peripheral nerves in periarteritis nodosa has been the subject of controversy for many years. One hypothesis holds that degeneration is due to anoxemia caused by closure or extreme narrowing of the nutrient vessels, an ischemic neuritis secondary to the arteritis. The other hypothesis states that the same unknown toxin or pathologic agent which affects the vessels acts independently on the nerve to produce primary degeneration. This hypothesis has had the larger number of proponents. Although the question has never been definitely settled, in recent years there has been an increasing tendency to regard the degeneration of nerves as being secondary to involvement of the nutrient arteries.

METHOD OF STUDY

This study is based on those cases of periarteritis nodosa observed at the Mayo Clinic from 1926 through 1946 in which the diagnosis was established or confirmed by postmortem examination. Strict criteria, both clinical and histologic, were used, all doubtful cases were eliminated. A total of 29 cases was studied, particular attention being directed toward the clinical and pathologic observations on the peripheral nerves.

Clinical Observations—The records of the 29 cases were carefully reviewed, primarily to determine the number which showed evidence of involvement of per-

TABLE 1—*Distribution of Cases by Number of Nerves Studied*

Nerves	No of Cases
1	3
2	4
3	5
4	4
5	3
6	2
7	1
8	1
12	1
15	1
Total	25

TABLE 2—*Number of Specimens of Each Nerve Studied*

Nerves	No of Specimens
Sciatic	40
Brachial plexus	23
Femoral	13
Radial	6
Ulnar	6
Median	6
Common peroneal	5
Posterior tibial	4
Phrenic	3
First digital	1
Recurrent laryngeal	1
Intercostal	1
Obturator	1
Sacral plexus	1
Total	111

ipheral nerves. Peripheral neuritis was diagnosed only on the basis of measurable changes in muscular strength, reflexes and sensory perception. All those patients considered to have peripheral neuritis showed localized muscular weakness, sensory changes alone were not deemed sufficient. Thus, those patients having only pain, or pain and tenderness, or even pain, tenderness and fleeting paresthesias were not included in the list of those who had neuritis. The group with peripheral neuritis was then compared with the nonneuritis group as to age, sex, duration of illness and presence or absence of the various clinical and laboratory signs. The records of those patients exhibiting involvement of peripheral nerves during the course of periarteritis nodosa were studied further to determine the mode and time of onset, location and type of involvement of nerves and factors of possible etiologic importance.

Pathologic Changes—The available peripheral nerves in all cases were studied, whether or not the patients had shown clinical evidence of neuritis. Of the total of 29 cases in which autopsy was performed, in 25 at least one peripheral nerve was removed for examination. The pathologic data, then, were accumulated from

the study of peripheral nerves from 25 cases of periarteritis nodosa. In most instances many more than one nerve were studied. A total of 111 nerves was examined in all. Table 1 shows the number of peripheral nerves obtained and studied in each case.

As would be expected, the peripheral nerves of the extremities were the most often studied, and the sciatic nerve the most frequently of all. In table 2 is shown a list of the nerves examined in the total series.

In most instances a portion of the nerve $1\frac{1}{2}$ to 2 inches (3.8 to 5 cm.) in length was removed at autopsy. Sections were then cut from one or more levels of this specimen. In a few cases it was possible to resect portions of the nerve at widely varying levels. Specimens of the sciatic nerve were obtained from the proximal portion of the nerve, before its emergence through the greater foramen.

In the study of a nerve at any one level, both transverse and longitudinal microscopic sections were made. All sections were routinely studied with hematoxylin and eosin, Verhoeff's stain for elastic tissue, Weigert's myelin sheath stain, the Mallory-Heidenhain stain and the Bodian silver impregnation method for staining axis-cylinders.

RESULTS

Clinical Study—The 29 patients ranged in age from $3\frac{1}{2}$ to 71 years, the average age was 44 years. There were 25 male and 4 female patients. The duration of illness varied from two weeks to twenty-nine months, the average duration of illness was 6.6 months. The blood pressure was elevated in 19 patients. Twenty-two of the patients showed elevations in temperature. The sedimentation rate was elevated in 20 of the 21 patients for whom that test was performed. Leukocytes numbered more than 12,000 per cubic millimeter of blood in 21 of the 27 patients in whom counts were made. Eosinophilia (3 per cent or more) was present in 7 patients. The 3 patients with most pronounced eosinophilia—73 per cent, 73 per cent and 57 per cent—had asthma as part of the clinical picture. Eight patients had a history of taking sulfonamide drugs shortly before the onset of the diseases. The causes of death were as follows: renal disease, 9 patients; cardiac conditions, 7; gastrointestinal disorders (hemorrhage or gangrene), 5; cerebral disorders, 5; respiratory failure, 2; and pneumonia, 1.

In 15 (52 per cent) of the 29 patients peripheral neuritis developed some time during the course of the illness. The group of 15 patients who had neuritis was compared with the group that did not have neuritis (14 patients). The average age of the patients with peripheral neuritis was 46.5 years against an average of 40.2 years for those without neuritis. There were 13 male and 2 female patients in the group in which neuritis developed and 12 male and 2 female patients in the group in which neuritis did not develop. The duration of periarteritis nodosa from onset of symptoms until death averaged 5.3 months in those with neuritis as against an average duration of eight months in those without. There was no significant difference between the two groups in the level or

frequency of hypertension, fever, leukocytosis or eosinophilia. The sedimentation rates did not differ significantly. Four patients in each group had a history of taking sulfonamide drugs before the onset. In those with neuritis, 4 showed a trace of lead in the urine and 2 of the 4 showed, in addition, a trace of arsenic. As might be expected, none of the patients without peripheral neuritis had the urine examined for toxic metals.

Further analysis of data on the group of 15 patients who had multiple peripheral neuritis was carried out. The results are presented in subsequent paragraphs.

Onset of Neuritis In 7 of the 15 cases, neuritis occurred at the onset of the disease, in other words, the periarteritis nodosa began as peripheral neuritis. In 3 cases, the neuritis occurred one month after the onset of the disease, in 2 cases, two months after the onset, in 2 cases, three months after the onset, and in 1, four months after the periarteritis nodosa first made itself known. In no instance was the appearance of the neuritis delayed longer than four months.

The initial neuritic symptoms were pain in 5 cases, paresthesias in 3, weakness in 2, pain and weakness in 2, pain and paresthesias in 2 and weakness and paresthesias in 1 case. The neuritis began in the lower extremities in 10 cases, in the upper extremities in 3 and in both upper and lower extremities in 2 cases.

Clinical Pattern In general, the peripheral neuritis tended to be widespread and severe. All four extremities were involved in 10 cases. In 2 cases, only the legs were affected, the arms only in 1, both arms and one leg in 1, and one arm and one leg in 1 case. In addition to the alterations in the nerves of the limbs, the phrenic nerves were involved in 2 instances, the cranial nerves in 1 and the bulbar portion of the brain stem in 1. The neuritis was severer peripherally than centrally in 14 of the 15 cases. The one exception was an instance in which the muscles of the pelvic and shoulder girdles were primarily affected. In 8 cases, the clinical picture was that of mononeuritis multiplex—involvement of several or many individual nerves at the same time, or at different periods in the course of the disease. In 7 instances, the clinical picture was that of a symmetric polyneuritis. Involvement of a single nerve, mononeuritis simplex, was not observed in this series.

The involvement was predominantly of the motor type. In 13 of the 15 cases both motor and sensory changes were present, in 2 there was only motor paralysis and in no case were there only sensory changes. Motor changes were more prominent than the sensory in 10 of the 13 cases showing mixed symptoms, in 3 the motor and sensory changes were approximately equal. In no instance were the sensory changes more prominent than the motor.

There was clearcut regression of signs and symptoms in 4 of the cases, in 11 the neuritis gradually or suddenly progressed or remained stationary until death from other cause

Histologic Study—Nutrient Arteries Involvement of the nutrient arteries of the peripheral nerves was observed in 19 (76 per cent) of the 25 cases studied In the 15 cases showing clinical peripheral neuritis, lesions of the nutrient arteries were observed in all (100 per cent) The vascular lesions were widespread, as evidenced by the fact that of the 111 individual nerves available for study, 80 (72 per cent) revealed such lesions In the 15 cases showing peripheral neuritis clinically, 69 (86 per cent) of the 80 nerves examined proved to have vascular lesions

The changes in the nutrient arteries of the nerves were in no way different from those caused by periarteritis nodosa in the other arteries of the body The vessels oftenest involved were the small arteries coursing in the interfascicular connective tissue In no instance was there involvement of the even smaller vessels within the nerve bundles The veins were not affected

The arterial lesions ranged from acute, through subacute and chronic stages, to instances of virtual healing The more acute lesions were characterized by a hyaline-like necrosis of the inner half of the media, degeneration of the remaining muscle fibers, dissolution of the internal elastic membrane, edema and thickening of the adventitia with infiltration by polymorphonuclear leukocytes, lymphocytes and eosinophils The subacute and chronic arterial lesions showed evidence of fibrous repair, splitting or actual overgrowth of the internal elastic membrane, fibrous thickening of the intima and periarterial infiltration by lymphocytes, plasma cells and large endothelial-like cells Healed lesions were noted in at least 1 case, these were characterized by replacement of normal tissue by fibrous tissue in the arterial wall, with scarring and thickening, recanalization of previously thrombosed lumens and disappearance of periarterial infiltration Regardless of the age of the degenerative inflammatory process, the chief functional effect was to reduce the caliber of the lumens of the involved vessels to a serious degree Many of the vessels were completely closed Thromboses in the narrowed lumens were common No aneurysms were noted in the vessels of the nerves, and no ruptures of the necrotic arterial walls with resultant intraneural hemorrhages were seen

Microscopic sections taken at different levels of a nerve often showed decided variation in the inflammatory processes in the arteries In some sections, almost every vessel was involved, while at a nearby level the arteries were essentially normal In a given nerve, it was not unusual to observe at different levels, acute, subacute and chronic arterial lesions

Nerve Degeneration Eleven (44 per cent) of the 25 cases studied showed microscopic degeneration of one or more nerves. All 11 cases in which there was degeneration of nerve bundles occurred in the group of 15 cases which showed peripheral neuritis (73 per cent). No clearcut degeneration of myelin sheaths and axis-cylinders was seen on histologic examination in those cases in which peripheral neuritis was not present. A total of 41 nerves was studied in which the inflammatory changes of periarteritis nodosa were observed in the nutrient arteries but in which no degeneration of nerve bundles was demonstrable. Thirty-nine nerves showed both inflammation of the arteries and degeneration of the nerve fibers. On the other hand, only 3 nerves were seen to be degenerated in which the vessels were apparently normal. Twenty-eight nerves were completely normal.

Study of the degenerated nerve bundles revealed subperineurial and interfascicular edema in many instances. The small endoneurial vessels within the fasciculi were sometimes widely dilated. In some cases, the degeneration varied from moderate to total destruction of the nerve elements with replacement by fibrous tissue. There was usually a great increase of the cells of the sheath of Schwann, though in old, degenerated nerves they were practically absent. In the moderate cases myelin sheath stains revealed that some nerve bundles were almost normal, while others were undergoing extensive degeneration, as evidenced by swelling, beading and disintegration of the myelin sheaths. Scavenger cells filled with fat droplets were seen along the course of the fibers. Silver impregnation (Bodian stain) brought out the appearance of the axis-cylinders, ranging from normal to complete disappearance. Many of the axis-cylinders were undergoing degeneration and were swollen, nodular, beaded and fragmented. In the severer cases, degeneration of the nerve elements was practically complete and only an occasional myelin sheath was to be seen. Regenerating axons were not observed. Degeneration was frequently minimal or even absent at the level of the severest vascular damage but became pronounced as more distal portions of the nerve were examined.

Diffuse degeneration of the neural elements as described in the preceding paragraph was not the only parenchymatous lesion observed. Striking, in some cases, was the occurrence of sharply localized infarcts, oftenest beneath the epineurium, but occasionally deep within the fasciculus. These infarcts in the more severely involved nerves were sometimes confluent. The level of the infarcts often coincided with the level of maximal vascular damage.

In no instance was there evidence of neuritis in the inflammatory sense. Despite the prominent perivascular collections of leukocytes and

exudate, no infiltration of these elements into the nerve bundles or around the nerve fibers was observed



Fig 1 (case 7) —Right sciatic nerve *A*, proximal portion showing subacute involvement of nutrient arteries, with almost complete occlusion of one of the vessels, hematoxylin and eosin, $\times 75$ *B*, almost complete degeneration of myelin sheaths at more distal level of nerve (right posterior tibial), Weigert's myelin sheath stain, $\times 435$

The arterial and neural lesions are illustrated in figures 1 through 5
A summary of the data for each case is given in table 3

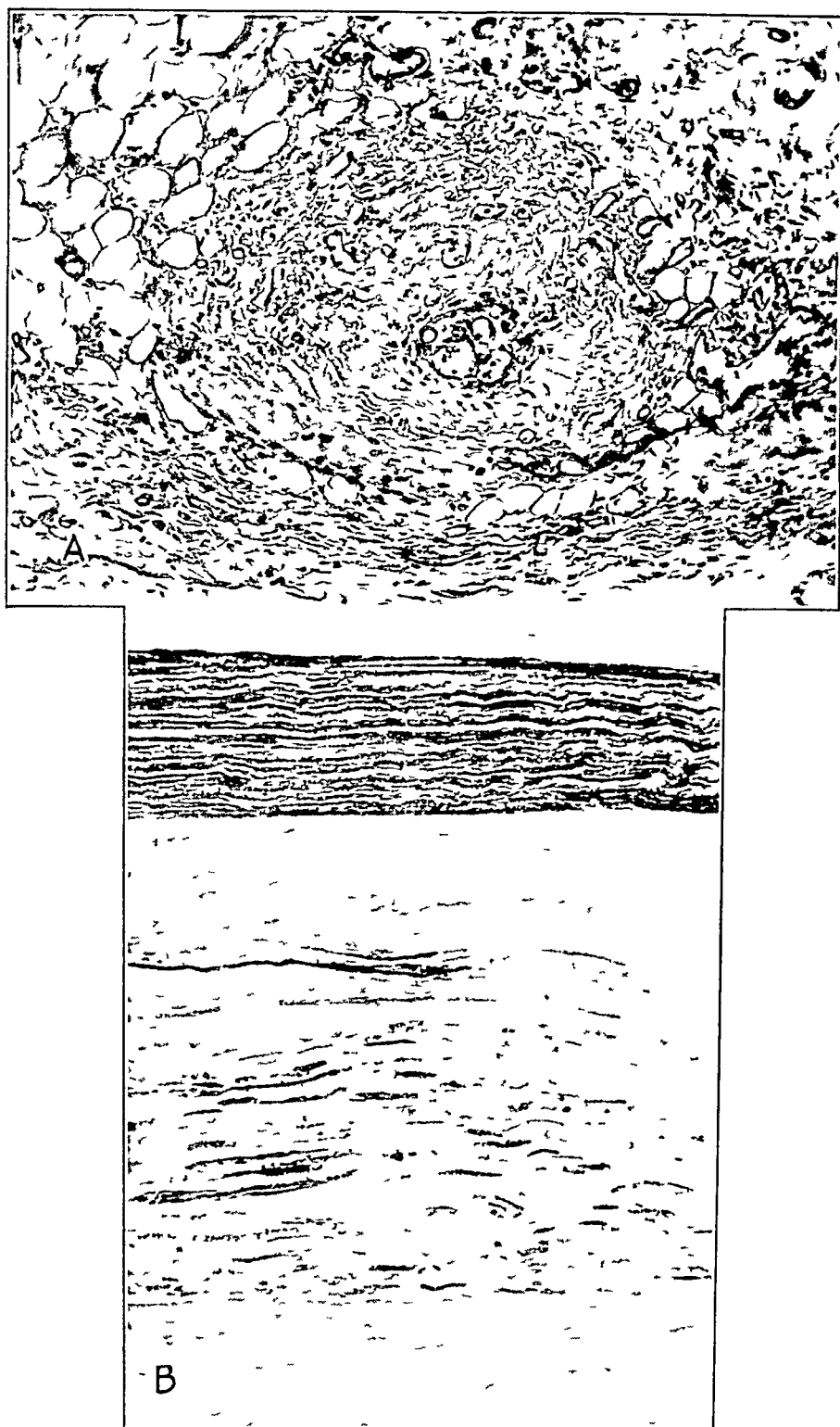


Fig 2 (case 8) —Right sciatic nerve *A*, nutrient artery, chronic stage, showing periarterial thickening and recanalization, hematoxylin and eosin, $\times 125$ *B*, same level as *A*, with marked degeneration of myelin sheaths. The upper nerve bundle is normal, Weigert's myelin sheath stain, $\times 60$



Fig 3 (case 25) —*A*, right sciatic nerve showing periarthritis of nutrient artery, acute stage, fibrinoid degeneration of media, with no peripheral neuritis despite widespread acute arterial changes, hematoxylin and eosin, $\times 150$ *B*, femoral nerve with longitudinal section of small nutrient artery showing rapid transition from acutely inflamed portion with necrosis of media to relatively normal vessel, hematoxylin and eosin, $\times 145$

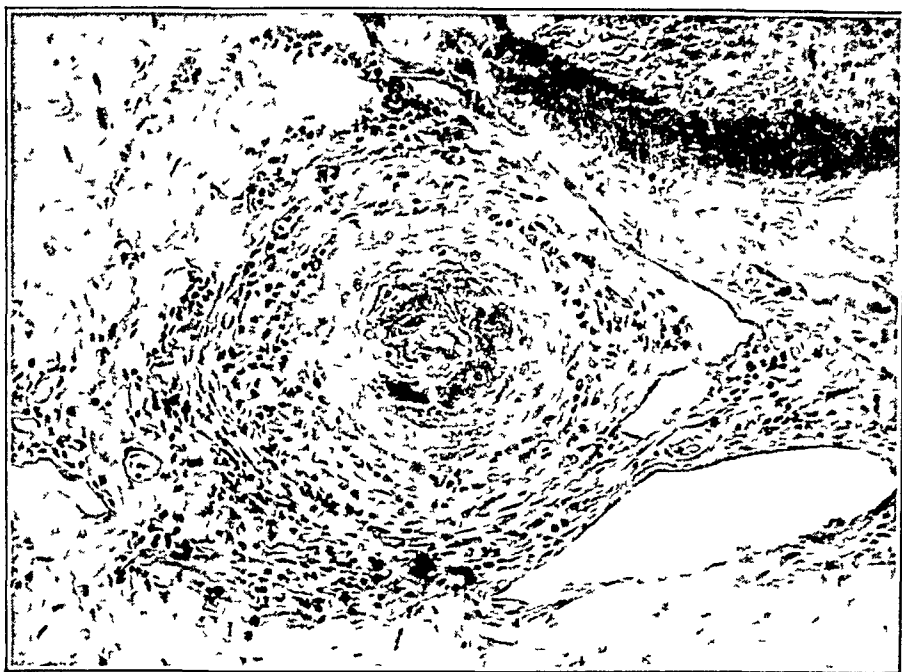


Fig 4 (case 25) —Femoral nerve showing acute fibrinoid degeneration of media with obliteration of lumen, hematoxylin and eosin, $\times 165$



Fig 5 (case 10) —Brachial plexus showing periarteritis of nutrient vessel, chronic phase, with recanalization, hematoxylin and eosin, $\times 125$

COMMENT

Analysis of the clinical data in 29 cases of periarteritis nodosa gave results which, for the most part, agreed closely with the mass of infor-

TABLE 3—Summary of Observations in 29 Cases of Periarteritis Nodosa

Case	Age yr	Sex	Dura- tion Mo	Blood pressure mm Hg Mercury	Sedimen- tation mm /Hr	Leukocytes mm ³ /mm ³	Eosino- phils %	Neuritis				Pathologic Processes	
								Present	Months After Onset of Disease	Classifi- cation ¹	Regres- sion	Arterial Changes	Nerve Deteri- oration
1	36	M	4	138/100	.	22	15	+	0	P	0	+	+
2	40	M	5	174/120		20	0	+	1	M	0	+	+
3	54	M	3	136/84	96	105	0	+	0	P	0	+	+
4	45	M	5	110/76	50	25	5	+	4	M	0	+	0
5	32	F	4	165/102		46	57	+	0	P	+	+	+
6	57	F	10	142/100	60	28	73	+	1	M	0	+	+
7	63	M	6	180/130	82	33	0	+	2	P	+	+	+
8	12	M	5	190/130	118	46	0	+	3	P	0	+	+
9	60	M	4	160/105	86	17	25	+	0	M	+	+	0
10	41	M	4	120/85	100	26	1	+	0	M	+	+	0
11	24	M	8	230/130	105	23	0	+	3	M	0	+	+
12	52	M	6	180/90	100	17	2	+	0	P	0	+	+
13	52	M	3	140/64	79	11	14	+	1	M	0	+	0
14	69	M	8	166/94	101	40	25	+	2	P	0	+	+
15	60	M	5	230/125	120	33	0	+	0	M	0	+	+
16	46	M	5	180/110		9	25	0				—	—
17	21	M	7	130/78	110	17	2	0				+	0
18	62	M	3	118/64	98	13	0	0				+	0
19	15	M	15	120/60	41	75	15	0				—	—
20	3½	F	5	100/60		16	0	0				0	0
21	66	M	2	146/80	6	65	0	0				0	0
22	46	M	8	255/150		11	0	0				—	—
23	35	M	27	120/96	41	24	73	0				—	—
24	71	M	½	120/80	67	17	0	0				0	0
25	25	M	3	144/108		21	0	0				+	0
26	46	M	6	220/130	85			0				0	0
27	32	F	29	230/130	72	18	3	0				0	0
28	61	M	1	230/150				0			—	+	0
29	59	M	1	220/130	94	24	0	0			—	0	0

*P indicates symmetric polyneuritic and M mononeuritis multiplex

mation already published. The sex ratio of 6:1 was somewhat greater than the 4:1 or 2.5:1 ratios usually given, but serves to stress further that the disease is definitely commoner in men than in women. It is

interesting that 3 of the patients presented the syndrome, previously described by Rackemann and Greene,¹⁰ of asthma associated with high eosinophilia. Although 8 patients were known to have taken sulfonamide drugs previous to the onset of the disease, information on that point was sketchy and incomplete. From these data no conclusions concerning the relation of sulfonamide compounds to the inception of periarteritis nodosa can be drawn.

Peripheral neuritis occurred in 52 per cent of the cases. This percentage is higher than that usually given, but probably represents a truer figure, for many authors observed that the incidence of neuritis is higher than available summaries indicate. It should be stressed that in some patients the presence of involvement of nerves is difficult to determine, especially in those who have purely subjective symptoms. In this study, however, strict criteria were met and the diagnosis of peripheral neuritis was not made unless objective signs were present. It so happened that in all patients who had neuritis, motor and reflex changes could be demonstrated. In not a few instances, the neurologist first suggested the eventual diagnosis. Comparison of the group of 15 patients in whom peripheral neuritis was present with the group of 14 in whom peripheral neuritis was not present demonstrated no essential differences in the results of laboratory studies or clinical course. The difference in average age, 46.5 years in those with neuritis versus 40.2 years in those without, is hardly of significance. The average duration of the disease in patients with neuritis was 5.3 months, while in those without, it was eight months. It is possible that the neuritis develops in the more acute cases, or that when neuritis does develop, the fatal outcome is hastened by the serious paralysis that sometimes ensues. The fact that 4 patients who had peripheral neuritis showed a trace of lead in the urine, and that 2 of the 4 also showed a trace of arsenic, is probably not significant. In no instance was the value even close to toxic levels. In this study attention was paid to the presence of heavy metals, not to cast doubt on the diagnoses, which were established at autopsy and unequivocal in all cases, but to try to determine whether subtoxic levels of agents known to be deleterious to peripheral nerves make them more vulnerable to another pathologic process. Unfortunately, no determinations were made on those patients without neuritis. The question, then, remains unanswered.

It is believed that the data obtained from the analysis of the clinical features of the 15 cases with peripheral neuritis will be of use in further delineation of the syndrome. In 7 of the 15 cases, the neuritic symptoms occurred at the onset of the disease before involvement of any other system. In no case did the neuritis appear longer than four months after

10 Rackemann, F. M., and Greene, J. E. Periarteritis Nodosa and Asthma, *Tr. A. Am. Physicians* 54: 112-118, 1939.

the onset of periarteritis nodosa. The commonest initial neurologic symptom was pain (5 cases), next in frequency as an initial symptom was paresthesia (3 cases). Though pain, paresthesia, or both, occurred most frequently at the onset, in 2 instances weakness alone was noted. The peripheral neuritis most commonly began in the lower extremities (10 cases).

The fully developed neuritis tended to be widespread and severe, the upper extremities were involved as often as the lower. In 10 cases all four extremities were affected. In all but one instance, the neuritis was severer peripherally than proximally. The motor involvement was more striking than the sensory, though usually both types were present. Two striking features of the peripheral neuritis in periarteritis nodosa were present in this series less commonly than had been previously reported. Other authors stated that the clinical picture is usually that of mononeuritis multiplex rather than that of multiple peripheral neuritis. In 8 of the 15 patients, several individual nerves were affected in sequence and at varying intervals—mononeuritis multiplex. But in the remaining 7, the pattern was that of a symmetric multiple neuritis which clinically was in no way different from that encountered in toxic or infectious polyneuritis. Why this should be so is not clear, but it is important to recognize that the pattern frequently occurs. It has been stated that regression is characteristic of the neurologic manifestations of periarteritis nodosa. Clearcut regression was evident in only 4 of the patients in this series. It must be remembered, however, that the average length of life after onset of symptoms was only 5.3 months. Had the patients lived long enough, more instances of regression would probably have been observed.

In a disease as unpredictable and as varied as periarteritis nodosa, all available evidence must be used in order to establish a diagnosis. The presence of peripheral neuritis is an important clue. Since it occurs in more than 50 per cent of cases, its presence should be of great help in formulating the diagnosis. In any obscure disease in which neuritis develops, periarteritis nodosa should be suspected. If the neuritis is associated with evidence of renal involvement, gastrointestinal symptoms, hypertension, fever and wasting, as it frequently is, the diagnosis becomes considerably less difficult. In view of the fact that periarteritis nodosa often begins as a peripheral neuritis, any patient with an obscure neuritis who later manifests multisystemic symptoms should be suspected of having that disease.

The cause and nature of the involvement of nerves have been subjects of controversy ever since periarteritis nodosa was first described. Whether the degeneration of the nerve is due to occlusion of its nutrient arteries, or to the direct action on the nerve fibers of the same toxin that causes

the changes in the arteries, is a question which has not been settled. Most authors favor the latter view. The present data indicate that the degeneration of nerves is entirely on a vascular basis, that localized infarcts in the more proximal portions of the nerve cause secondary degeneration of the fibers and, therefore, the appearance of diffuse degeneration in the more distal portions. In all 15 cases with clinical peripheral neuritis, changes typical of *periarteritis nodosa* were observed in the nutrient arteries to the nerves. In 11 of the 15 cases, degeneration of the nerves was demonstrated microscopically. It is felt that nerve degeneration was not seen in the additional 4 cases because only the proximal portions of the nerves were available for study. Eighty individual nerves were studied in the 15 cases with neuritis, 69 of them showed lesions of the *arteriae nervorum* and 42 of them showed degeneration. In 39 of the 42 nerves with degeneration, the nutrient arteries were involved, in 3 of the nerves with degeneration, no inflamed vessels were seen. It is not surprising that these 3 exceptions occurred, since *periarteritis nodosa* affects only a small portion of any one vessel and the distribution of the lesions is notoriously patchy. It so happened that the sections did not pass through an involved vessel. That *periarteritic* vessels were seen in 39 of the 42 nerves showing degeneration is indicative of the fact that the vascular lesions are usually exceedingly widespread. It should be remembered that even when a portion of a nerve is thoroughly studied, actually only a small fraction of its total length has been examined. In 39 of the 80 nerves the nutrient arteries were involved, but no degeneration was demonstrable. It is probable that in these instances the lumens of the inflamed vessels were still able to carry a sufficient volume of blood, so that infarction and subsequent degeneration did not take place. No degenerated nerves were seen in the group of 14 cases without neuritis, though 11 of the 31 nerves studied showed inflammation of the nutrient arteries.

The blood supply to nerves is relatively rich. Sunderland¹¹ showed that the peripheral nerves are abundantly vascularized through their entire length by a series of vessels, which, by their repeated division and anastomoses, create an unbroken longitudinal, intraneural vascular network. Any single nutrient artery, or a series of them, can be occluded without embarrassing the blood supply to the nerve. When the arterial tree is normal, the sciatic nerve can be stripped of its blood supply for a distance up to 15 cm without impairment of nerve function. Despite this rich blood supply to the peripheral nerves, it has been shown that occlusive vascular disease, especially when it is widespread, can cause anoxic changes in the conducting elements of the nerve, with the production of clinical neuritis. Thus, the peripheral neuritis of senility

11 Sunderland, S. Blood Supply of the Sciatic Nerve and Its Popliteal Divisions in Man, *Arch Neurol & Psychiat* 54: 283-289 (Oct.) 1945

can be caused by arteriosclerotic changes in the nutrient arteries¹² There is strong evidence that at least one type of diabetic neuritis is caused by the same mechanism¹³ Ischemic neuritis also has been reported in thromboangitis obliterans¹⁴ and in primary amyloidosis¹⁵ There seems little reason to doubt, then, that periarteritis nodosa, a disease causing severe and widespread arterial damage, can also produce ischemic neuritis Since periarteritis nodosa is known to cause infarctions in practically every organ of the body, it would be most unusual for the nerves to escape, especially since it has been shown that the arteriae nervorum are so commonly and markedly involved

That histologic examination of the peripheral nerves did not reveal any instance of primary or interstitial neuritis is significant Signs of inflammation in the nerve bundles were completely lacking This observation is not in keeping with what one would expect if the degeneration of nerves was due to direct action by the same agent which produced disease in the vessel wall

SUMMARY AND CONCLUSIONS

1 Peripheral neuritis occurred in 15 of 29 cases of periarteritis nodosa in which the diagnosis was proved at necropsy

2 Peripheral neuritis usually appeared early in the course of the disease The initial symptoms of neuritis were most commonly pain, or pain and paresthesia The neuritic manifestations initially occurred most commonly in the lower extremities

3 Neuritis in periarteritis nodosa tended to be widespread and severe Motor involvement was more striking than sensory involvement The classic picture of mononeuritis multiplex occurred in 8 of the 15 cases Regression took place in only 4 of the 15 cases

4 A comparison of the group in which peripheral neuritis occurred with the group in which peripheral neuritis did not occur revealed no significant difference in age incidence, prognosis or laboratory findings during the course of the disease

5 Histologic examination of the peripheral nerves was carried out in 25 of the 29 cases of periarteritis nodosa

12 Oppenheim, H I Ueber die senile Form der multiplen Neuritis, *Berl klin Wchnschr* 30 589-592 (June) 1893

13 Woltman, H W, and Wilder, R M Diabetes Mellitus Pathologic Changes in the Spinal Cord and Peripheral Nerves, *Arch Int Med* 44 576-603 (Oct) 1929

14 Barker, N W Lesions of Peripheral Nerves in Thrombo-Angitis Obliterans A Clinicopathologic Study, *Arch Int Med* 62 271-284 (Aug) 1938

15 Kernohan, J W, and Woltman, H W Amyloid Neuritis, *Arch Neurol & Psychiat* 47 132-140 (Jan) 1942

6 The arteriae nervorum were directly involved by the disease process in 19 (76 per cent) of the 25 cases. The nutrient arteries to the nerves were affected by periarteritis in all 15 cases showing peripheral neuritis clinically (100 per cent).

7 Microscopic degeneration of nerve bundles was demonstrated in 11 of the 15 patients with peripheral neuritis. No degenerated nerves occurred in the group without clinical neuritis.

8 Single or confluent infarcts of the nerve bundles were commonly observed. The degeneration, which was diffuse at lower levels, began as infarction at higher levels. There was no inflammation in any of the nerves.

9 The degeneration of the peripheral nerves is due to occlusion of the nutrient vessels to the nerves. The peripheral neuritis in periarteritis nodosa is an ischemic neuritis.

Mayo Clinic

SEVERE HYPERLIPEMIA ASSOCIATED WITH NONDIABETIC PREGNANCY

Report of a Case

CAPTAIN ROBERT J ROHN
CAPTAIN CHARLES GANDEK
AND

CAPTAIN MAX D BARTLEY
Medical Corps, United States Army

HYPERLIPEMIA associated with lipemia retinalis occurs rarely Stearns and his associates¹ in a recent publication, after thorough search of the literature, reported a total of 63 cases of retinal lipemia involving diabetic patients, including their own reported case, and 6 involving nondiabetic patients Kauffman² reported 61 cases of retinal lipemia in diabetic patients and 3 in which the condition was not associated with diabetes

Cases of lipemia retinalis in nondiabetic patients reported were as follows Wagener³ reported a case of lipemia retinalis in which the patient, who had leukemia, was receiving high doses of radium, and it was his opinion that the high fat content was due to destruction of tissue Holt⁴ reported the case of an 11 year old girl in whom the blood lipids rose to levels above 8,000 mg per hundred cubic centimeters He also noted that the girl's 5 year old brother had lipemia retinalis with abnormal fat metabolism and that their mother had abnormally high blood fat levels although she was never found to have retinal lipemia This, Hold felt, represented an idiopathic familial deficiency in fat storage Goodman⁵ and Chapman⁶ reported a case of nondiabetic lipemia retinalis in a 1 year old child, which Chapman ascribes to absence of lipase result-

1 Stearns, S , Friedman, E , Lugitch, M, and Hoffman, S H Lipemia Retinalis, New England J Med **238** 16-17, 1948

2 Kauffman, M L Lipemia Retinalis, Am J Ophth **26** 1205-1208, 1943

3 Wagener, H P Lipemia Retinalis, Am J Ophth **5** 521-525, 1922

4 Holt, L E, Jr , Aylward, F X, and Timbrus, H G Idiopathic Familial Lipemia, Bull Johns Hopkins Hosp **64** 279-314, 1939

5 Goodman, M , Shuman, H, and Goodman, S Idiopathic Lipemia with Secondary Xanthomatosis Hepatosplenomegaly and Lipemia Retinalis, J Pediat **16** 596-606, 1940

6 Chapman, F D, and Kinney, T D Hyperlipemia "Idiopathic Lipemia," Am J Dis Child **62** 1014-1024 (Nov) 1941

ing in deficient fat fermentation of fat storage. The sixth case of lipemia was reported by Lepard,⁷ in which lipemia retinalis was observed over a period of years. The abnormal fatty metabolism was controlled by a rigid diet, although it was not entirely obliterated. No conclusions were made by Lepard as to the mechanism of abnormality of fat metabolism in this case. However, he noted, as did Chapman, the relatively greater increase in the size of the spleen as compared to the size of the liver.

The milky blood serum and the unusual appearance of the retinal vessels⁸ form a striking picture which cannot be missed. It is the retinopathy which gives the name of lipemia retinalis to the disease process. It is noted by a survey of the literature that lipemia retinalis usually accompanies acidosis either of diabetes or of other toxic states, but acidosis is not an invariable prerequisite of lipemia retinalis, as has been noted.⁹

Stearns¹ stated that lipemia retinalis may be present for two days to three weeks. Kauffman² also reported that the condition is fleeting, lasting for only one to ten days. However, Holt⁴ observed retinal lipemia for several months in his case, and in Lepard's case⁷ the condition persisted for over a period of several years.

The case which we here present has several unusual features. It is the only case in which lipemia retinalis is reported complicating a pregnancy in a nondiabetic patient. It is the second case in which autopsy was performed while the disease was active. The blood fats reached levels higher than those in the cases reported with the exception of Holt's.⁴ For these reasons it was thought of sufficient interest to report the findings.

REPORT OF A CASE

On Oct. 7, 1947, a 19 year old woman in the eighth month of her pregnancy was admitted to the medical service for investigation. Several weeks prior to her admission milky blood serum was noted when attempts to perform the routine serologic tests were made. As far as could be ascertained by her history, it was the first time that this had been noted. She was completely asymptomatic, her pregnancy had been previously uneventful and she complained of no intolerance to food or loss of weight. The history by systems was noncontributory. Her last menstrual period occurred on Feb. 3, 1947.

Physical examination revealed a height of 65 inches (165 cm.) and a present weight of 148 pounds (67 Kg.) as opposed to a normal weight of 125 pounds (56.7 Kg.). The blood pressure was 124 systolic and 78 diastolic. The skin was completely clear, showing no discoloration or exanthema. The external appearance of the eyes was normal. Funduscopic examination revealed abnormally pale

7 Lepard, C. E. Lipemia Retinalis in Nondiabetic Patient, *Arch. Ophth.* 32:37-38 (July) 1944.

8 Duke-Elder, W. S. *Text-Book of Ophthalmology*, St. Louis, C. V. Mosby Company, 1941, vol. 3, p. 2742.

9 Boyd, E. M. Lipid Composition of "Milky" Blood Serum, *Tr. Roy. Soc. Canada* 31:11-16, 1937. Kauffman² Wagener³ Holt, Aylward and Timbrus⁴ Goodman, Shuman and Goodman⁵ Chapman and Kinney⁶

fundi The veins were slightly engorged and were chocolate in color The arteries appeared flat and ribbon-like In the periphery, arteries were uniformly cream colored Near the disk the vessels had a central "salmon pink-colored" blood column, surrounded by the cream-colored fatty substance floating nearest the vessel wall No hemorrhages or exudates were seen The disk was slightly paler than normal, the macular area was normal Abdominal examination revealed a mass compatible with an eight month pregnancy The liver, which was firm and had a sharp edge, was palpable approximately 2 cm below the costal margin

The laboratory reports were as follows Red blood cells numbered 4,300,000, with a hemoglobin content of 12 Gm, and the white blood cells 12,600, with neutrophils 61 per cent, stab forms 16 per cent, lymphocytes 18 per cent and monocytes 5 per cent Red and white blood cells showed numerous small vacuoles The sedimentation rate was 28 mm per hour as corrected The hematocrit value was 27 per cent packed cells Urinalysis gave a negative reaction The initial fasting blood sugar content was 67 mg per hundred cubic centimeters Cholesterol was 248 mg per hundred cubic centimeters The carbon dioxide—combining power was 82.1 per cent A recheck of the blood showed a cholesterol content of 411 mg per hundred cubic centimeters, a carbon dioxide—combining power of 54 per cent, a fasting blood sugar content of 70 mg per hundred cubic centimeters A glucose tolerance test revealed a fasting blood sugar content of 87 mg, which rose in one-half hour to 130 mg, in one hour to 135 mg and in two hours to 146 mg and fell in three hours to 98 mg Urinalysis revealed a negative reaction at all times Chemical examination of the blood by the Army Medical Department Research and Graduate School on Oct 20, 1947, revealed the following Neutral fat amounted to 3.837 Gm, phospholipids 26.6 mg, total cholesterol 488 mg, free cholesterol 196 mg and cholesterol esters 291 mg per hundred cubic centimeters Blood specimens were sent to the New York Postgraduate Medical School's laboratory of pathological chemistries on Oct 27, 1947, and the following values were obtained total serum lipids, 8,288 Gm, fatty acids, 7,685 mg, phospholipids, 7.5 mg, cholesterol, 760 mg, and cholesterol esters, 430 mg Roentgen examinations of the chest showed no abnormality In the skull the calvarium and basila were normal, as were the bony structure and the texture of both femurs

During the patient's stay on the medical service, she remained asymptomatic, and, aside from a low fat, high carbohydrate diet, she received no specific therapy Basal metabolism rates were determined, and values +10 and +21 per cent were revealed The patient was seen by two civilian consultants to the Surgeon General's Office, Dr R Miller and Dr Bruce Webster It was their opinion that she had essential lipemia, with a possible abnormal response to the frequently noted abnormal fat metabolism of pregnancy An initial smear of the peripheral blood showed numerous fat vacuoles in the red blood cells and in the cytoplasm of the white blood cells In addition, wandering reticuloendothelial cells with ingested fat particles made up 4 per cent of the cells in smears of the peripheral blood To rule out the diagnosis of leukemia, examination of sternal marrow was performed, which showed hyperplasia of all elements of the blood but no evidence of leukemia Noted were normal-appearing plasma cells containing ingested fat globules which represented no more than 2 per cent of the total marrow constituents Because of the apparent normal progression of pregnancy, it was decided that the patient should be allowed to go to term, to have a normal delivery and to see if on the termination of pregnancy her metabolism would return to normal On the day that she was to be discharged, cramping abdominal pains developed, and she was transferred to the Tilton Obstetrical Service She had one episode of nausea and one loose stool Approximately fifteen hours after the onset of labor she

complained of different, excruciating abdominal pain and went into profound shock. At this time fetal heartbeats disappeared and were not heard subsequently. She was given plasma, which improved her blood pressure and the clinical picture, and Major Brenizer, Assistant Chief of Surgical Service, was called in consultation. Because of the possibility of an intraperitoneal hemorrhage or an acute hemorrhagic pancreatitis, surgical exploration was performed. The possibilities of multiple renal or mesenteric vessel emboli or thromboses, lipid coronary insufficiency or lipid pulmonary emboli were considered. The laparotomy was performed under local anesthesia. When the abdomen was opened, large volumes of milky, cloudy, dark pink odorless fluid escaped under moderate pressure, 750 cc of this fluid was aspirated. The stomach was filled with fluid and tensely dilated. The transverse colon was infiltrated with sanguineous fluid, and the whole root of the mesentery was thick and edematous, the liver appeared slightly enlarged and infiltrated with lipid material. The pancreas appeared normal, and it was felt that nothing could be done surgically. Dr. Preece, the civilian gynecology consultant, felt that since the membranes had been ruptured and in view of her critical condition hysterectomy should not be performed. The abdomen was carefully closed with layered sutures. Postoperatively she had to be maintained on large amounts of oxygen to prevent development of severe cyanosis. Administration of 5 liters of whole blood was necessary to maintain her peripheral circulation. Approximately ten hours postoperatively she spontaneously delivered a stillborn, full term infant, which showed no abnormalities other than overlapping of the cranial sutures and a few scattered blebs over the neck and trunk. In spite of all supportive measures, her course was downhill. Her abdomen became distended with fluid, her peripheral circulation failed, and eighteen hours postoperatively she died—twenty-seven days after her admission to the hospital.

Autopsy was performed, and the positive findings were as follows. There was cyanosis of the nail beds. Two thousand five hundred cubic centimeters of bloody fluid was released from the peritoneal cavity. The entire serosa of the small bowel and the large bowel was pale brown and studded with creamy fibrinous attachments. The whole retroperitoneal area was filled with dark brown, stringy blood clots, which dissected the transverse colon's mesenteric attachment, converting the tissue-thin mesentery into a thick boggy mass. No lymph nodes were discernible. The thyroid weighed 18 Gm, the thymus was grossly normal. Hilar nodes were normal. The heart and the coronary vessels and the aorta and its main branches were grossly normal except for small petechial hemorrhages beneath the epicardium. The spleen was enlarged, weighing 750 Gm, slate gray and gritty and did not scrape easily. The weight of the liver was 2,140 Gm. Cut section of the liver displayed a light brown color and a greasy consistency. The gallbladder and the bile ducts were grossly normal. Just above the entrance of the splenic vein and into the portal vein there was a firmly adherent grayish red area of thrombosis, 3 cm in length, tapering off into the vessel of the hepatic substance. The pancreas was moderately enlarged and on cut section was firm, fibrotic and pale. The adrenals could not be located in the massive blood clot. The bowel and genitourinary tract were not remarkable except for the findings compatible with postpartum and postoperative conditions. On microscopic examination, the following was noted. Liver sections showed some lymphocytic infiltration around the bile ducts and central veins. Fatty infiltration was minimal in amount. Some extracellular and intracellular pigmentation was present. The pancreas showed extensive diffuse necrosis throughout. Some areas of necrosis had vague remnants and outlines of pancreatic tissue, and near the head of the pancreas there was heavy fibrosis, with considerable diminution in glandular structure and few islet

cells The parietal cells of the gastric mucosa were vacuolated In the small intestine the villi were distended with numerous swollen lymphatic vessels which could be traced into the submucosa The spleen showed complete loss of normal architecture, which was replaced by a diffuse pattern of round cells with centrally placed nuclei These foam cells were aggravated in some portions of the section The remainder of the pathologic examination revealed nothing significant in relation to the disease process

Autopsy was performed on the infant, and the findings were completely normal

COMMENT

It is a matter of some disappointment to the medical service that certain procedures, which should and could have been performed, were not accomplished because no such rapid and fatal outcome was anticipated With such data as we have available, several remarkable features can be noted We were unable to obtain any relatives of the patient for study of their fat metabolism to rule out absolutely congenital lipemia Her completely noncontributory personal history, the significant phagocytic blood response and the coincidence of the discovery of her disease at the time of pregnancy are strong presumptive evidence that the disease was at least aggravated if not initiated by her pregnancy It is an established fact that pregnancy results in an increased metabolism of fat

The relationship of the pancreatic changes to this abnormal fat metabolism is obscure The acute pancreatitis might in some way be linked to the thrombosis of the portal vein, the anoxemia or the shock, but it is difficult to reconcile the chronic fibrosing pancreatitis with any features of the patient's clinical history or the laboratory findings It is of great interest to note that Holt⁴ reported that his patient at the age of 4 years had an attack of acute epigastric pain for which a laparotomy was performed and a postoperative diagnosis of acute hemorrhagic pancreatitis was made The girl had repeated recurrent attacks of acute epigastric abdominal pain associated with a picture of shock similar to that noted in our case Kauffman,² in his second case report, stated that a laparotomy was performed to rule out the possibility of a pancreatic tumor He made no note, however, of the operative findings or of the result of any possible biopsy The association between the lipemia and the pancreatitis in our case seems to be definitely present It is impossible to explain the mechanism by which the two are related to each other on the basis of our findings It is entirely possible that the fibrosing pancreatitis resulted in a deficiency of lipase, with a resulting deficient fermentive system in the organs of fat storage such as was noted by Chapman⁶

Most observers noted a relative decrease in the phospholipid fraction They, however, noted an absolute increase In the initial report in this case the phospholipid content is only 26.6 mg per hundred cubic

centimeters The second report showed that total lipids amounted to 8,288 mg , fatty acids, 7,685 mg , cholesterol, 760 mg , cholesterol esters, 430 mg , and phospholipids 75 mg per hundred cubic centimeters This is considered to be close to the lowest limits of normal This well substantiates the conclusion of Boyd⁹ that phospholipids tend to maintain the other fat fractions in a supersaturated state in serum and when the phospholipid content of the serum diminishes the lipids come out of solution as chylomicrons, forming a milky emulsion This also offers a partial explanation of the long duration of the lipemia retinalis in this case

We have no explanation of the diminution of the phospholipid content There was no diabetic acidosis and no previous vomiting, marasmus gastritis or faulty nutrition¹ We can only speculate on the possible effect of pregnancy on metabolism of phospholipids Because of the unfortunate death of the patient and her child, further phospholipid studies were not available Such studies in pregnancy may reveal important information for advancement pertinent to the disease process Because of the obscure origin of the disease process in this case, it was extremely difficult to work out any logical management The usual measures of a low fat, high carbohydrate diet had no demonstrable effect on the course of the disease It is suspected that the uterine contractions with the inevitable alteration in vascular mechanics, might have propagated a fat embolism which initiated the portal vein thrombosis In retrospect, we wonder if early termination of pregnancy by section might have changed the ultimate outcome of events It would certainly have increased the chances of a living infant, and it might have meant the survival of the mother

SUMMARY

The seventh case of lipemia retinalis in a nondiabetic patient is presented It is the first case of lipemia retinalis associated with pregnancy that has been reported The disease is a result of increased serum lipids, with a relative decrease in serum phospholipids resulting in milky serum and colorless retinal vessels The possible relationship of the disease to pregnancy is noted, and the suggestion that cesarian section might be employed for such a complication of pregnancy is offered

Dr M Luther Kauffman personally communicated with us concerning his experience with the disease Captain Lovitt, Chief of Laboratory Service, studied the pathologic specimens, and Captain Fontana, Chief of the Obstetrical Service, and Major Brenizer, Assistant Chief of the Surgical Service, managed the obstetric and surgical aspects of the case presented

PRIMARY BRONCHOGENIC CARCINOMA

Correlation of Recent Literature with One Hundred and
Thirty-One Proved Cases

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IT IS WELL substantiated that the mortality rate of primary cancer of the lung has reached major proportions¹ This disease, which in the not too distant past was regarded as unusual in occurrence, is now rated as fifth in frequency in types of carcinoma among males,² and proportionately as constituting 10 per cent of all deaths due to cancer³ As recorded in "Vital Statistics of the United States," based on the number per hundred thousand population, the death rate in 1920 was 1.1, in 1930, 2.2, in 1940, 4.0, in 1943, 7.3, and in 1944, 7.9⁴ The last figure represents 10,537 deaths due to carcinoma of the lungs and pleura

Figures reported in various statistical studies bear a great deal of similarity It is of paramount importance, in this respect, to note the absolute, as well as the relative, increase in the incidence of this disease⁵ Universally, this increase is accredited to earlier recognition based on advanced methods of diagnosis, education of the medical profession and "cancer consciousness" in the public⁶

From the Department of Radiology, Philadelphia General Hospital

1 (a) Deaths and Death Rates for Cancer and Other Malignant Tumors, Vital Statistics of the United States, United States Department of Commerce, Bureau of the Census, 1944 (b) Macklin, M. T. Has Real Increase in Lung Cancer Been Proved? *Ann Int Med* 17:308 (Aug) 1942

2 Holinger, P. H., Hara, H. J., and Hirsch, E. F. Bronchogenic Carcinoma. An Analysis of One Hundred and Seventy-Five Proved Cases, *Ann Otol, Rhin & Laryng* 54:5 (March) 1945

3 Ochsner, A., and DeBakey, M. Surgical Considerations of Primary Carcinoma of the Lung, *Surgery* 8:992 (Dec) 1940

4 (a) Footnote 1a (b) Holinger, Hara and Hirsch²

5 (a) Holinger, Hara and Hirsch² (b) Ochsner and DeBakey³ (c) Perone, J. A., and Levinson, J. P. Primary Carcinoma of the Lung (Report of One Hundred and Fifteen Cases, Thirty-Eight Autopsies and Seventy-Seven Bronchoscopic Biopsies), *Ann Int Med* 17:12 (July) 1942

6 Clerf, L. H. Carcinoma of the Bronchus, *Radiology* 28:438 (April) 1937

Additions to the diagnostic armamentarium have been few, but, together with improvements in technic and refinements in interpretation of studies, have greatly increased the possibility of earlier diagnoses. In spite of these diagnostic advancements, the early recognition of primary bronchogenic carcinoma has not kept pace with the almost phenomenal strides made in the surgical technic of cancer of the lung, and the proportion of operative cures maintains a relatively low level.⁷

This paper is a correlation study of the recent literature, together with observations on 131 cases of primary bronchogenic carcinoma at the Philadelphia General Hospital between the years 1940 and 1946, inclusive, with a parallel evaluation of the progress made in the diagnosis and management of the disease.

TABLE 1—*Comparative Distribution in Three Series of Cases*

	Hollinger and others ²		Perrone and Levinson ^{5c}		O'Keefe	
	No	Per Cent	No	Per Cent	No	Per Cent
Right lung ..	3	1.7	0	0	3	2.3
Left lung ..	2	1.1	0	0	4	3.3
Main bronchus of right lung ..	55	31.4	6	7.7	23	17.5
Main bronchus of left lung ..	20	11.4	7	9.7	11	8.3
Upper lobe of right lung ..	19	10.8	13	16.6	9	6.8
Upper lobe of left lung ..	15	8.5	4	5.2	25	19.0
Lower lobe of right lung ..	32	18.2	34	44.1	19	14.4
Lower lobe of left lung ..	23	13.1	9	11.6	27	20.6
Middle lobe of right lung ..	2	1.1	2	2.3	10	7.6
Lower lobe of both lungs ..	4	3.0	1	1.4	0	0
Middle and lower lobes of right lung ..	0	0	1	1.4	0	0
	175		77		131	

STATISTICAL STUDY

The statistical data reported show the following characteristics of bronchogenic carcinoma. It is predominantly a disease of white men, its greatest incidence is between the ages of 45 and 60, it has a definite predilection for the right lung, the average length of life in cases in which the patient is not amenable to surgical cure is twelve to eighteen months.⁸

In the present series of 131 patients, 125 were men and 6 were women, or a proportion of 20:1, there were 82 patients between the ages of 50 and 70, an incidence of 62.5 per cent in this age group. Subsequent to diagnosis, 111 patients, or 84.7 per cent, died within eighteen months. The only deviation from the accepted figures noted in this study is the

7 Ochsner, A, and DeBakey, M. Significance of Metastasis in Primary Carcinoma of the Lungs, *J Thoracic Surg* 11:357 (April) 1942.

8 (a) Hollinger, Hara and Hirsch.² (b) Ochsner and DeBakey.³ (c) Perrone and Levinson.^{5c} (d) Clerf.⁶ (e) Ochsner and DeBakey.⁷ (f) Overholt, R. H. Curability of Primary Carcinoma of the Lung. Early Recognition and Management, *Surg, Gynec & Obst* 70:479 (Feb, no 2A) 1940. (g) Clerf, L. H., and Herbut, P. A. Bronchogenic Carcinoma, *Am J Med* 1:168 (Aug) 1946.

almost equal distribution between the left and the right lung, the carcinoma occurring in the right lung in 63 cases and in the left lung in 68 cases

The cardinal symptoms of bronchogenic carcinoma, in the order of frequency of occurrence, are recorded as cough, pain in the chest, expectoration and dyspnea. The fact that this sequence frequently is not evident in specific instances is the cause of occasional controversy.

The histopathologic picture presented is predominantly that of epidermoid carcinoma, with an occasional report of adenocarcinoma. Convincing evidence of the bronchiolar origin of the "alveolar cell tumor" was submitted in reports by Herbut⁹. In the present series of 131 cases, the tumor was of the squamous cell variety in 114 and of the adenomatous type in 17 cases—a proportion of 67:1.

ETIOLOGY AND SYMPTOMATOLOGY

In evaluating the causes of cancer of the lung, it is immediately apparent that no one makes so bold as to attempt to name the basic etiologic factor. Writers agree as to the importance of chronic irritants as essential contributing and predisposing factors,¹⁰ but, as Clerf and I stated previously in discussing the etiologic factors in malignant disease of the sinuses, "malignant disease . . . may be the result of a peculiar type of metaplasia associated with the repair of epithelium destroyed by disease. Evidently this statement is not all-inclusive, for such accidents as cell rests, dermoids, and epithelial extensions must be given equal consideration."¹¹ This similarly, represents the basic pathologic changes occurring in repair of the bronchial mucosa in malignant disease of the lung.

Holinger and his associates² reviewed the secondary etiologic factors in a recent paper. In their analysis of such inhalation irritants as coal dust, silica, exhaust gases, road tar and tobacco smoke, they concluded that "without further corroborative evidence, (these) too, must be considered coincidental." Clerf and Herbut^{8g} placed a unique and pertinent interpretation on the relationship of tobacco smoke: "Irrespective of its being an etiological factor, smoking, more than anything else, contributes

9 Herbut, P. A. (a) Bronchiolar Origin of "Alveolar Cell Tumor" of the Lung, *Am J Path* 20:911 (Sept.) 1944, (b) "Alveolar Cell Tumor" of the Lung. Further Evidence of Its Bronchiolar Origin, *Arch Path* 41:175 (Feb.) 1946.

10 (a) Holinger, Hara and Hirsch² (b) Perrone and Levinson^{5c} (c) Clerf⁶ (d) Clerf and Herbut^{8g}

11 O'Keefe, J. J., and Clerf, L. H. Malignant Tumors of the Maxillary Sinus. An Analysis of Forty-Seven Fatalities, *Ann Otol, Rhin & Laryng* 55:312 (June) 1946.

to delay in diagnosis by masking a common, early and important symptom namely, cough”

Clinical manifestations of this disease usually are not evident until after the primary lesion has undergone moderate growth. The majority, of squamous cell type, manifest symptoms through invasion of regional tissue, producing secondary factors, such as erosion and ulceration of the mucosa, bronchial obstruction with retained secretions, secondary infection, atelectasis and/or compression of one of the larger pulmonary vessels. Tumors originating in the extreme periphery, the “alveolar cell



Fig 1—Metastatic cervical adenopathy with ulceration in a case of primary bronchogenic carcinoma

tumors,” are more apt to produce symptoms referable to the pleura, or to the remote organs by metastases¹². Too often, both types produce metastatic lesions before adequate consideration has been given the symptoms caused by the primary lesion of the lung.

In general, early symptoms of primary bronchial carcinoma are those common to all disease of the upper respiratory tract, but not necessarily so. Since the site of origin may be in any part of the bronchial system, the symptoms produced show a great tendency to variability and multiplicity, further masking is produced by those parenchymal lesions (alveolar cell tumors) that rapidly metastasize and cause focal symptoms in remote viscera. In the same paper, Holinger and his associates,² reporting

12 Holinger, Hara and Hirsch² Ochsner and DeBailey⁷ Herbut^{9b}

on 175 cases, stated "there is no group of symptoms, either subjective or objective, that is pathognomonic," but that "fully 98 per cent of the symptoms are referred to the chest" Yet, in 21.7 per cent of 60 cases of bronchial carcinoma studied by Hochberg and Lederer¹³ there were no symptoms referable to the chest This variability in recorded statistics is noted elsewhere in the literature and only lends emphasis to the facts (1) that the symptoms of early bronchogenic carcinoma follow no stereotyped pattern, (2) that every symptom referable to the chest reported by the patient should be considered as organic in origin and (3) that investigation should be pursued until an accurate diagnosis is attained

The development and presence of detectable physical signs, on the other hand, are evidences of advanced growth, and almost invariably

TABLE 2 —*Symptoms on Patient's Admission to the Hospital*

	No	Per Cent
Cough	100	76.3
Thoracic pain	82	62.5
Sputum	74	56.4
Dyspnea	52	39.6
Hemoptysis	51	38.9
Loss of weight	48	36.6
Loss of strength	42	32.0
"Cold"	35	26.7
Night sweats	10	7.6
Hoarseness	10	7.6
Wheezing	3	2.2

preclude the possibility of operability Obvious tumor formation in the thoracic wall, paralysis of the vocal cords, pathologic fracture of the ribs, esophageal dysfunction and/or persistent pleural pain, all carry the label of "inoperability"

Numerical tabulation of symptoms reported shows that cough is the most important single symptom¹⁴ It is usually dry and irritative, gradually changing to the productive type, soon to be associated with blood streaking The disease being commonly interpreted as tuberculosis throughout this stage, much valuable time is spent in the disproving of such a diagnosis Next frequently reported is the symptom of thoracic pain This may be one of two types a constricting sensation, similar to that associated with obstructive atelectasis, or the sharp, lancinating pain of pleurisy, due to pleural or subpleural extension of a peripherally situated lesion This combination of cough and thoracic pain, associated with other evidences of infection of the respiratory tract, has resulted in the diagnosis of "cold," "grip," "influenza" or "pneumonia" in a large percentage of cases Likewise, the sequence of pneumonia, "unresolved

13 Hochberg, L. A., and Lederer, M. Early Manifestations of Primary Carcinoma of the Lung, *Arch. Int. Med.* 63:80 (Jan.) 1939

14 Holinger, Hara and Hirsch;² Ochsner and DeBailey;³ Perrone and Levinson;^{5c} Clerf;⁶ Clerf and Herbut;^{8a} Hochberg and Lederer;¹³

pneumonia" and pulmonary suppuration is commonly elicited in the history

Dyspnea and loss of weight become evident as the lesion develops. Progressive or gradually developing dyspnea is a manifestation if infiltration and/or bronchial obstruction occurs, and is seen in instances of atelectasis, pleural effusion, bilateral involvement or compression of the pulmonary arteries or veins. On the other hand, acute dyspnea associated with pain in the chest is most frequently caused by the development of spontaneous pneumothorax. Dyspnea of long duration is soon associated with extreme physical fatigue and results in anorexia and loss of weight. This symptom, of moderate or long duration, carries a poor prognosis.

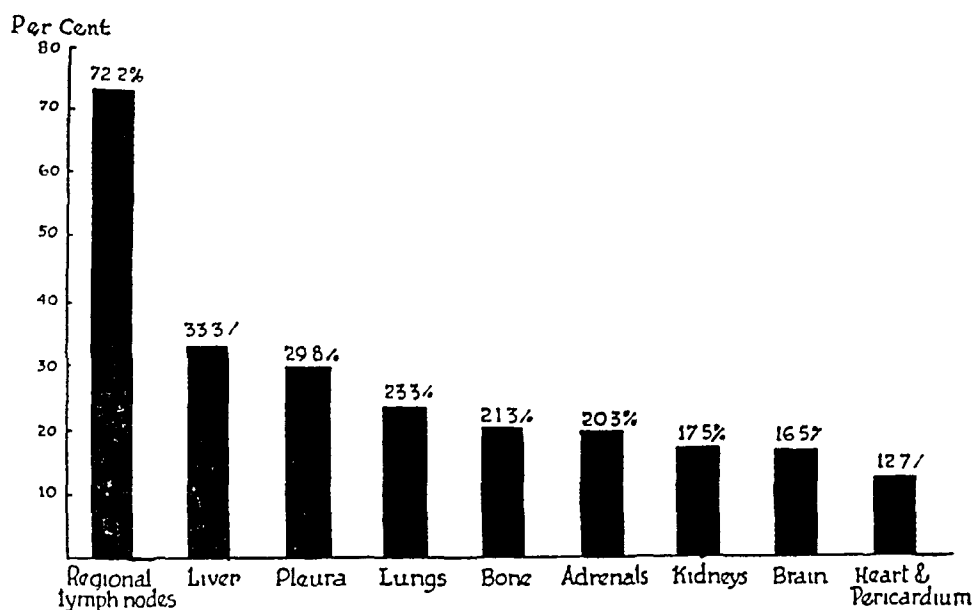


Fig. 2.—Incidence of metastasis in a large number of collected cases (from Ochsner and DeBakey⁷)

Wheezing respiration is frequently not reported by the patient because often it is of brief duration and intermittent. It is affected by cough and deep respiration, and forced expiration aids greatly in its demonstration.⁸⁵ It is significant evidence of partial obstruction of a bronchus, caused either by direct encroachment on the lumen or by extrabronchial compression stenosis.

Other symptoms follow in variable sequence: massive pulmonary hemorrhage, paralysis of the vocal cords, causing hoarseness, dysphagia, caused either by mediastinal compression or by secondary esophageal growth, convulsions, or paralysis of central origin—all part of the portrait of advanced bronchogenic cancer.

The symptoms of metastatic lesions may appear bizarre and confusing. Not infrequently such foci are the first to manifest symptoms, and their

camouflage may keep the primary disease well hidden Ochsner and DeBakey⁷ stated that “ in 50 autopsy cases studied by Rogers, this occurred in 44 per cent, and in 9 per cent of the 72 cases analyzed by King” Occasionally it is only through the study of metastatic lesions that one is directed to the site of the primary disease Thus, the same writers concluded “It becomes apparent, therefore, that an adequate conception of metastasis and the methods of spread in primary bronchogenic malignancy is of diagnostic, prognostic, and therapeutic importance and deserves serious consideration” The authors further showed the unusually widespread sites of involvement, so that “ no part of the body is immune to metastatic invasion”



Fig 3—Roentgenograms illustrating the value of oblique and lateral views in diagnostic roentgenography A, posteroanterior view, B, oblique view The arrow points to an area of encroachment on the tracheal lumen

DIAGNOSTIC METHODS

Roentgenology—The roentgenogram is probably the most valuable single means of obtaining an early presumptive diagnosis of bronchogenic carcinoma The use of this facility in mass surveys of the chest, initially intended as a check for the presence of tuberculosis, has proved equally valuable in detecting the presence of malignant growths and of other pulmonary disease Many persons with a pulmonary neoplasm when so observed have been free from symptoms—the ideal stage at which to make a diagnosis and to institute treatment However, several weaknesses in the application of the roentgenologic method are apparent, and this criticism is pertinent A single roentgenogram is often not sufficient especially if limited to a posteroanterior view, initial negative reports

are considered as final, and, because of a false impression or a mistaken original diagnosis, reevaluation is not attempted until much time has elapsed

Early developing densities in the lung fields follow no form or pattern Their outlines are indistinct and their margins irregular It is axio-



Fig 4—*A*, showing an area of segmental atelectasis of the lower lobe of the right lung *B*, after instillation of iodized oil, showing the bronchial obstruction which caused atelectasis Cytologic study of bronchoscopically removed secretions revealed carcinoma cells

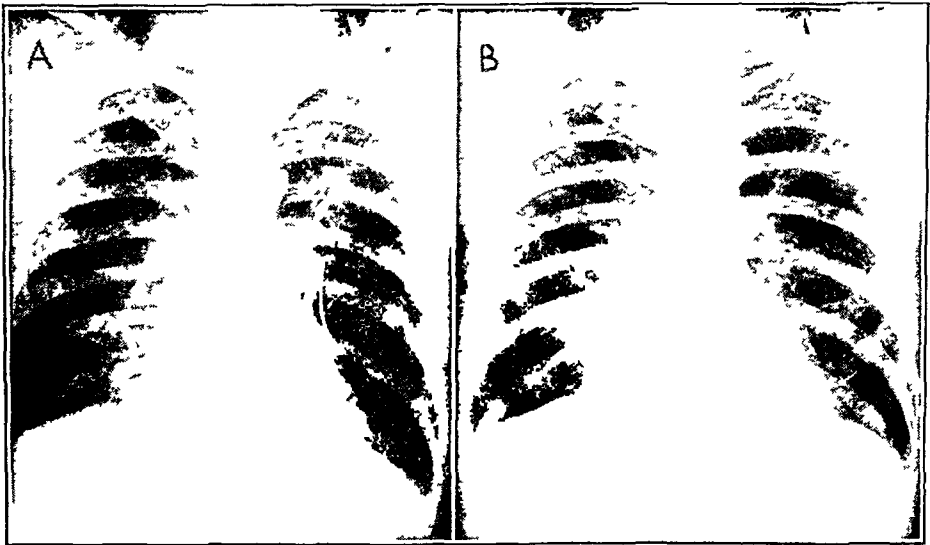


Fig 5—Roentgenograms illustrating value of reexamination of a patient with a poorly defined pulmonary shadow *A*, area of increased density radiating upward from the hilus of the left lung, *B*, made fourteen days later, revealing a normal state In the interim, two bronchoscopic examinations, including studies for carcinoma cells, gave negative results

matic that the only thing typical about them is that they are atypical. Roentgenographic examination may well be misrepresented if made casually or "routinely" in these early cases. As the lesions grow, complicating factors develop—bronchial obstruction, retained secretions and secondary infection. These are manifested in the picture of obstructive emphysema in cases of partial obstruction, and of obstructive atelectasis in cases of complete obstruction, drowned lung, bronchiectasis and sepsis.

One should appreciate the fact that the interpretation of a roentgenogram in cases of early bronchogenic cancer depends on, or is influenced by, the extent of the primary growth and the presence or absence of these secondary morphologic alterations. Small shadows, situated peripherally, with a tendency to clear, only to recur, are in all probability neoplastic (fig 5). Larger lesions may cause partial bronchial obstruction and appear as obstructive emphysema, may undergo central necrosis and appear as an abscess or obstruct the drainage of secretions and appear as bronchiectasis. As reported by Farrell¹⁵ in 1936, it still holds that the commonest roentgenologic manifestation of total bronchial obstruction is

TABLE 3—*Method of Establishing Diagnosis in 131 Cases of Primary Bronchogenic Carcinoma*

	No	Per Cent
Bronchoscopic biopsy	68	51.9
Bronchoscopic aspiration of secretions	4	3.0
Bronchoscopy, showing morphologic alterations	20	15.4
Roentgenography	12	9.1
Autopsy	20	15.4
Biopsy of metastatic nodes	4	3.0
Aspiration of pleural fluid	1	0.8
Needle aspiration biopsy	1	0.8
Exploratory thoracotomy	1	0.8

atelectasis of the segment, lobe or lung tissue distal to the tumor. Although these cases of complete obstruction present a wide variability of roentgenographic observations, it is evident that the commonest diagnostic signs in bronchogenic carcinoma are those produced by varying degrees of bronchial obstruction.

Further information is sometimes obtained in a roentgenographic study by the use of such special procedures as planography and bronchography. Both these procedures may add corroborative evidence to the presence of suspected intrabronchial or extrabronchial tumor.

Bronchoscopy—The indication for diagnostic bronchoscopy consists in the presence of bronchopulmonary symptoms, the explanation of which is incomplete or unsatisfactory. This policy is the reversal of that originally practiced by those who developed the technic of bronchoscopy, but during this formative period one had to feel reasonably certain of

¹⁵ Farrell, J. T., Jr. Diagnosis of Bronchial Carcinoma. Clinical and Roentgenologic Study of Fifty Cases, *Radiology* 26:261 (March) 1936.

the nature of the pulmonary disease before attempting a bronchoscopic examination, then, too, the results secured through this practice were obtained only to substantiate the previously made clinical diagnosis. The technic of this procedure has reached suitable refinement so that today bronchoscopic examination is made, not to substantiate the obvious, but as a means of ascertaining the diagnosis.

Bronchoscopic study should be made in all cases of suspected bronchogenic carcinoma, as evidenced clinically by persistent cough, pain in the chest, wheezing or hemoptysis, in cases in which the presence of neoplasm is based on the roentgenologic findings or in those in which obscure pulmonary symptoms are manifested. Yet, in the face of such a wide range of indications, bronchoscopic examination is often deferred or is not utilized at all.

Views of bronchogenic carcinoma obtained bronchoscopically are variable. The tumor is usually nodular, is soft and red, often ulcerated and bleeds at the slightest trauma. Associated with this ulcerated tumor

TABLE 4—*Time Between Initial Symptoms and Hospitalization*

Number of Cases	Period
29 (22.1%)	More than one year
24 (18.3%)	Six months to one year
78 (59.5%)	Less than six months

TABLE 5—*Incidence of Roentgenologic and Histologic Diagnosis in 131 Cases of Primary Bronchogenic Carcinoma*

Roentgenologic Incidence		Histologic Incidence	
Positive	70 (53.4%)	Positive	98 (74.7%)
Indefinite or false	22 (16.7%)		
No report	39 (29.7%)	No report	33 (25.2%)

is a variable amount of infiltration and rigidity of the bronchial walls, extending at times far proximal to the tumor. Such lesions offer no difficulty to the securing of a positive biopsy diagnosis. Other lesions, especially those situated at the extreme periphery or in the upper lobe, are infrequently capable of visualization bronchoscopically, and the telescopic insert rarely adds significant information. However, when the lesion is associated with induration or distortion of the bronchial walls, causing disruption of the normal physiologic activity of the bronchus, one may presume that the disease is malignant. It is because of this type of lesion that further means of diagnosis must be devised and employed in order to secure an earlier positive histologic diagnosis.

Such means include aspiration biopsy and exploratory thoractomy. These have both enjoyed an initial period of enthusiastic approval, although of recent years much controversy has arisen as to the practicability

of the continued use of biopsy by aspiration¹⁶ The proverbial "two schools of thought" each have several prominent advocates, but the method has lost much favor, owing to the fear of implantation metastases in the track of the aspirating needle To balance the scale, the

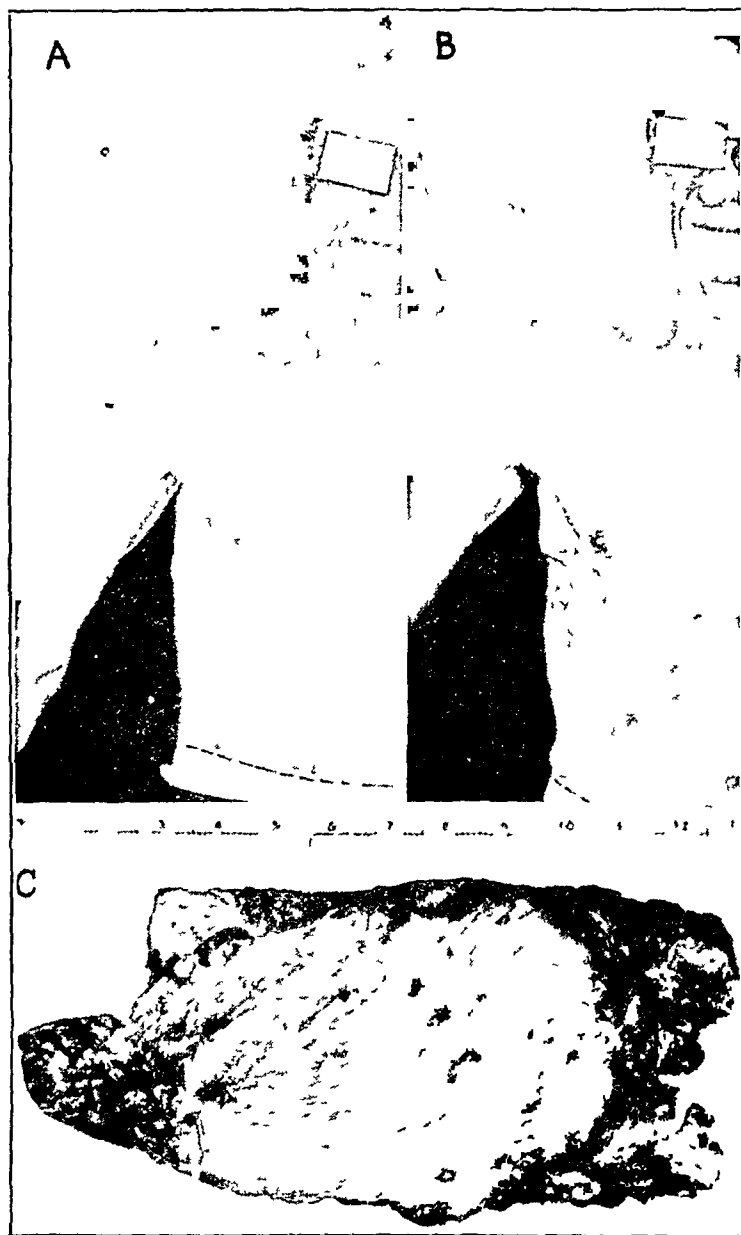


Fig 6—A, photograph of pneumonectomized patient, showing development of implant metastases in the chest wall at the exact site of aspiration for biopsy B, photograph of the patient after excision of the lesion C, photograph of the tumor removed from the chest wall (Photographs provided by Dr Frank F Allbritten Jr)

16 (a) Ochsner, A, Dixon, J L, and DeBakey, M Primary Bronchiogenic Carcinoma, *Dis of Chest* 11 97 (March-April) 1945 (b) Craver, L F Diagnosis of Malignant Lung Tumors by Aspiration Biopsy and by Sputum Examination, *Surgery* 8 947 (Dec) 1940

practice of exploratory thoracotomy has gained universal widespread favor, as pointed out by Churchill, Graham, Ochsner, Overholt and others. However, even this practice has its shortcomings, for at the time of thoracotomy the nature of a small centrally placed lesion is indistinguishable from an area of organized pneumonitis, an abscess or an anthracotic or silicotic nodule.

Most recently developed, and of excellent promise, is the practice of cytologic study of bronchoscopically removed secretions. With the aid of the Papanicolaou technic of staining cytologic secretions,¹⁷ this procedure has added a high percentage of positive results in the early diagnosis of primary bronchogenic cancer. Herbut and Clerf,¹⁸ reporting on this method, emphasized its particular usefulness in treating lesions that are located peripherally and in which endoscopic exposure is not feasible. In the summary of their paper they stated:

In 30 consecutive cases of primary pulmonary carcinoma, bronchial secretions were stained by the Papanicolaou technic. Cancer cells were demonstrated in 22 cases, or 73 per cent. In the same series a positive morphologic diagnosis, from a study of tissue removed endoscopically, was obtained in 11 cases, or 36 per cent. Cancer cells were present in the secretions from 7 cases in which bronchoscopy was negative.

Sputums were examined from 5 cases in which cancer cells were present in bronchial secretions, and in only 1 of these were neoplastic cells found. We therefore believe that examination of bronchial secretions for tumor cells is superior to examination of sputum.¹⁸

It is apparent that the application of this method of investigation is of particular significance in the study of those lesions that are peripherally situated and bronchoscopically inaccessible. The added percentage of positive histologic diagnoses so obtained promises to increase the recognition of early bronchogenic carcinoma by an appreciable margin. Its practice, too, is free of the dangers, real or imaginary, that are integral parts of the technic of aspiration biopsy and thoracotomy.

MANAGEMENT

The therapeutic approach to carcinoma of the lung, as with carcinoma in any other part of the body, is dependent on the extent of involvement at the time of diagnosis, and, by virtue of this fact, must be defined as either palliative or definitive—as a form of palliation in cases in which the neoplasm is beyond hope of cure, as definitive therapy in those in which the tumor is considered early and operable.

17 Papanicolaou, G. N., and Traut, H. F. *Diagnosis of Uterine Cancer by the Vaginal Smear*, New York, The Commonwealth Fund, 1943.

18 Herbut, P. A., and Clerf, L. H. *Bronchogenic Carcinoma*, J. A. M. A. 130: 1006 (April 13) 1946.

Both approaches to therapy have at their disposal three methods of attack bronchoscopic, by removal of tissue with forceps or by electrocoagulation or by both, roentgenologic, in the form of high voltage irradiation or of implantation of radon seeds or radium directly into the tumor tissue, and surgical, by extirpation of the diseased organ

That the treatment of bronchogenic carcinoma is primarily surgical, there is no argument But the management of a patient entails far more than surgical consideration alone

Bronchoscopy—Bronchoscopy as utilized in the treatment of bronchogenic carcinoma should be considered as a means of therapy of patients with lesions otherwise inoperable or as preoperative therapeutic measure in cases with obstructive phenomena Its use as a definitive form of therapy for the so-called benign adenoma of the bronchus or in cases of a proved malignant growth supposedly limited to the bronchial lumens is no longer looked on as proper¹⁹ An abundance of instances are cited in the literature regarding treatment of the so-called benign adenoma of the bronchus by bronchoscopic means Specific clinical cures were reported by Kernan,²⁰ Jackson, Konzelmann and Norris,²¹ Ormerod,²² and others, by use of this method together with electrocoagulation However, there is reason to suspect the classification of this type of tumor as benign, since many pathologists consider the benign adenoma of the bronchus a carcinoma of low grade malignancy or as maintaining the potentiality of becoming malignant²³ Graham and Wolmack^{19a} asserted that this "benign" lesion was a "potentially malignant tumor," and Alexander²⁴ called it a "carcinoma of low grade malignancy" Regardless of the exact identity of this type of tumor, relief of bronchial obstruction and removal of retained secretions preparatory to its surgical extirpation constitute the procedure of accepted practice

19 (a) Graham, E A, and Womack, N A The Problems of the So-Called Bronchial Adenoma, *J Thoracic Surg* 14 106 (April) 1945 (b) Chamberlain, J M, and Gordon, J Bronchial Adenoma Treated by Pulmonary Resection, *ibid* 14 144 (April) 1945

20 Kernan, J D Treatment of a Series of Cases of So-Called Carcinoid Tumors of the Bronchi by Diathermy A Report of Ten Cases, *Ann Otol, Rhin & Laryng* 44 1167, (Dec) 1935

21 Jackson, C L, Konzelmann, F W, and Norris, C M Bronchial Adenoma, *J Thoracic Surg* 14 98 (April) 1945

22 Ormerod, F C Malignant Disease of the Bronchus, *J Laryng & Otol* 48 733 (Nov) 1933

23 Clerf, L H, and Bucher, C J Adenoma (Mixed Tumor) of the Bronchus A Study of Thirty-Five Cases, *Ann Otol, Rhin & Laryng* 51 836 (Sept) 1942

24 Alexander, J Discussion on Symposium of Bronchial Adenoma, *J Thoracic Surg* 14 122 (April) 1945



(See legend on opposite page)

In those instances of a proved malignant growth in which surgical intervention is contemplated, bronchoscopy as a preoperative adjunct again occupies a definite place in the management of the patient. A relatively clean lung, one free of retained secretions, is less apt to contaminate the pleural cavity at the time of operation than is a lung that has not had the benefit of bronchoscopic aspiration prior to operation. Too, a patient freed of the toxic effects of this infected secretion is a better surgical risk.²⁵

Patients with inoperable carcinomas are likewise maintained in a better state of health through bronchoscopic drainage and are given relief from the symptoms of obstruction. The patients are thereby supported during their period of radiation therapy.

Irradiation—For many years radiation therapy has been looked on as the panacea in the treatment of bronchogenic carcinoma. Early writings were highly enthusiastic in its praise. With the passage of time and a more detailed follow-up study of the case, a truer evaluation of the efficiency of irradiation shows that it is neither a panacea nor of particular value as curative or palliative therapy. These facts are brought out in the writings of Steiner,²⁶ Bloch and Bogardus,²⁷ Widmann,²⁸ and others.²⁹ It is generally conceded that primary bronchogenic carcinoma is a highly radioresistant neoplasm, and, although regression or arrest of growth may be affected initially, it is almost impossible to administer a completely carcinocidal dose.

Irradiation of endobronchial lesions by the bronchoscopic insertion of radon seeds or radium needles is a recent development in the field of

25 Harrington, S. W. Pneumonectomy for Carcinoma of the Lung, *J Thoracic Surg* 11 357 (April) 1942.

26 Steiner, P. E. Effects of Roentgen Therapy on Histologic Picture and on Survival in Cases of Primary Carcinoma of the Lung, *Arch Int Med* 66 140 (July) 1940.

27 Bloch, R. G., and Bogardus, G. Bronchogenic Carcinoma, with Special Reference to Results with Roentgen Therapy, *Arch Int Med* 66 39 (July) 1940.

28 Widmann, B. P. Roentgen Therapy for Bronchiogenic Cancer, *Am J Roentgenol* 51 61 (Jan) 1944.

29 Pohle, E. A., and Siris, E. L. Roentgen Rays in the Treatment of Carcinoma of the Bronchus. An Analysis of Sixty-Nine Cases Treated in the State of Wisconsin General Hospital from 1933 to 1943, *J Thoracic Surg* 13 67 (April) 1944. Shenstone, N. S. Experiences with Total Pneumonectomy, *J Thoracic Surg* 11 405 (April) 1942.

radiation therapy³⁰ The results of this form of therapy are generally conceded to be palliative in effect, and its use is limited to patients with lesions considered otherwise inoperable

Surgical Therapy—That only a scant number of patients with a lesion diagnosed as primary bronchogenic carcinoma can be helped by operation is attested to by all who have intimate dealings in this field Watson, cited by Pohle and Siris,²⁹ stated that only 26 per cent of these patients are in any way fit for surgical treatment Churchill reported that the tumor was operable in 33.6 per cent of 155 cases, and Brock,⁷ in 12.3 per cent of 106 cases Similarly, all show that this percentage is cut far more than one half by those cases in which the tumor was seen to be inoperable at the time of exploratory thoracotomy³¹

The technical difficulties in thoracic surgery have been almost completely overcome Problems of anesthesia and of control of hemorrhage and sepsis are no longer of serious consequence The surmounting of these technical obstacles has broadened the scope and application of thoracic surgery, so that today patients with cancer of the lung of questionable operability demand the right to exploratory thoracotomy It is generally credited to the thoracic surgeons that there is no more danger of opening the chest than there is of opening the peritoneal cavity

In excellent papers on the technic of lung surgery for bronchogenic cancer, such writers as Ochsner and DeBakey, Harrington and Overholt advocated the procedure of total pneumonectomy,³² insisting that lobectomy is fraught with the danger of leaving as residuals carcinomatous cells in the lymphatic channels of the lung tissue Their statistics support this view entirely

The number of five year cures reported varies from 3 to 7 per cent of the total number of cases in which the tumor was considered operable at the time of surgical intervention That this number amounts to an infinitesimal part of the total number of cases in which the diagnosis is made is no reflection on the surgeons They, in accord with the clinicians and bronchoscopists, recognize that the only way to increase this percentage is by furthering efforts toward earlier diagnoses

30 Pressman, J. J., and Emery, C. K. A New Method of Radium Application in Cancer of the Bronchus, *Ann. Otol., Rhin. & Laryng.* 46:314 (June) 1937

31 (a) Ochsner and DeBakey⁷ (b) Overholt, R. H., and Rumel, W. R. Clinical Studies of Primary Carcinoma of the Lung. An Analysis of Seventy-Five Cases, Twenty-One of Which Were Treated by Pneumonectomy or Lobectomy, *J. A. M. A.* 114:735 (March 2) 1940 (c) Harrington²⁵ (d) Bloch and Bogardus²⁷

32 Ochsner and DeBakey⁷ Harrington²⁵ Overholt and Rumel^{31b}

SUMMARY

One hundred and thirty-one cases of proved primary bronchogenic carcinoma are analyzed and correlated with the data in the recent literature

Statistics support the view that the incidence of this disease is absolutely, as well as relatively, increasing. Characteristically, it is predominantly a disease of white men, its greatest incidence occurs between the ages of 45 and 60, it has a definite predilection for the right lung, and the average length of life of patients not amenable to surgical treatment is twelve to eighteen months.

Notable among the efforts to secure earlier diagnosis is the development of the technic of cytologic study of bronchoscopically removed secretions, this practice promises to increase the recognition of early cancer of the lung by an appreciable margin.

Management of patients with this neoplasm entails the evaluation of several factors: the location and degree of extension of the primary growth, the presence or absence of secondary obstructive phenomena and the presence or absence of detectable metastatic lesions. Therapy has at its disposal three methods of attack: bronchoscopic, roentgenologic and surgical. Surgical extirpation of the involved lung is the only method offering possible cure.

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LIABILITY OF ADDICTION TO 6-DIMETHYLAMINO-4-4-DIPHENYL-3-HEPTANONE (METHADON, "AMIDONE" OR "10820") IN MAN

Experimental Addiction to Methadon

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AFTER the invasion of Germany by the Allied armies, a Department of Commerce intelligence team¹ which investigated the German pharmaceutical industry found that the chemists of the I G Farbenindustrie had developed a potent synthetic analgesic drug, 6-dimethylamino-4-4-diphenyl-3-hepatone, which bore the serial number 10820² Investigation of the pharmacology of the drug in the United States showed that many of its actions resembled closely the actions of morphine in both animals³ and man⁴ The question of the liability of

From the Research Department, United States Public Health Service Hospital

1 Kleiderer, E C , Rice, J B , Conquest, V , and Williams, J Pharmaceutical Activities at the I G Farbenindustrie Plant, Hoechst Am Main, Report 981, Office of the Publication Board, United States Department of Commerce, July 1945

2 The drug has also been referred to in the United States as "dolophine," AN-148, anadon or "amidone" The name methadon has been assigned to the compound by the Council on Pharmacy and Chemistry of the American Medical Association (Methadon, Generic Term for 6-Dimethylamino-4, 4-Diphenyl-3-Heptanone, report of the Council on Pharmacy and Chemistry, J A M A 134 1483 [Aug 23] 1947) and will be used throughout this paper

3 (a) Scott, C C , and Chen, K K The Action of 1,1-Diphenyl-1-(Dimethylaminoisopropyl)-Butanone-2, a Potent Analgesic Agent, J Pharmacol & Exper Therap 87 63-71 (May) 1946 (b) Wikler, A , Frank, K , and Eisenman, A J Effects of Single Doses of 10820 (4-4-Diphenyl-6-Dimethylamino-Heptanone-3) on the Nervous System of Dogs and Cats, Federation Proc 6 384 (March) 1947 (c) Eddy, N B Personal communication to the authors (d) Karr, N W Effects of 6-Dimethylamino-4, 4-Diphenyl-3-Heptanone (Dolophine) on Intestinal Motility, Federation Proc 6 343 (March) 1947 (e) Haag, H B , Finnegan, J K , and Larson, P S Pharmacologic Observations on 1,1-Diphenyl-

addiction to the drug was therefore immediately raised. It is the purpose of this paper to present the results of studies on the liability of addiction to methadon which were carried out on former morphine addicts who volunteered for the experiments. In these studies particular attention was paid to the qualities which Himmelsbach⁵ regards as characteristic of addiction to a drug: tolerance, physical dependence and habituation (psychologic or emotional dependence).

A few studies on the development of tolerance to various actions of the drug have already been carried out. Scott and Chen^{3a} noted that tolerance to the sedative and narcotic actions occurred when dogs were given a single daily dose of the drug intraperitoneally for twenty-eight days. However, tolerance to the analgesic effect of the drug (as measured by the Andrew's⁶ modification of the Hardy-Wolff-Goodell thermal radiation method) did not develop. In later studies, Scott, Kohlstaedt, Robbins and Israel^{3f} found that tolerance to the pain-threshold-elevating action of the drug developed in dogs if several doses were given daily. Wikler and Frank⁷ demonstrated the appearance of tolerance to the analgesic effect, as measured by the tooth pain reaction technique, in dogs receiving four doses of methadon per day. Eddy^{3c} found that partial tolerance to the analgesic action developed in mice after they received 5 mg of methadon per kilogram of weight subcutaneously for twenty-eight days. Wikler and Frank⁷ have recorded the development of tolerance to the sedative and narcotic effects and the action on the reflexes of the paralyzed limbs in dogs with chronic spinal disease. Isbell, Wikler,

1-(Dimethylaminoisopropyl)-Butanone-2, *ibid* 6 334 (March) 1947 (f) Scott, C C, Chen, K K, Kohlstaedt, K G, Robbins, E B, and Israel, F W. Further Observations on the Pharmacology of 'Dolophine' (Methadon, Lilly), *J Pharmacol & Exper Therap* 91 147-156 (Oct) 1947

4 (a) Isbell, H, Wikler, A, Eisenman, A J, and Frank, K. Effects of Single Doses of 10820 (4-4-Diphenyl-6-Dimethylamino-3-Heptanone-3) on Man, *Federation Proc* 6 341 (March) 1947 (b) Kirchhof, A C, and David, N A. Clinical Trial of a New Synthetic Heptanone Analgesic ('Dolophine'). I Preliminary Report, *West J Surg* 55 183-186 (March) 1947 (c) Troxil, E B. The Analgesic Action of 1,1-Diphenyl-1-(Dimethylaminoisopropyl)-Butanone-2 in Man, *Federation Proc* 6 378 (March) 1947. Scott and Chen^{3a}

5 Himmelsbach, C K, and Small, L F. Clinical Studies of Drug Addiction. II "Rossium" Treatment of Drug Addiction, with a Report on the Chemistry of "Rossium," Supplement 125 to the Public Health Reports, United States Treasury Department, Public Health Service, 1937, pp 1-18

6 Andrews, H L, and Workman, W. Pain Threshold Measurements in the Dog, *J Pharmacol & Exper Therap* 73 99-103 (Sept) 1941

7 Wikler, A, and Frank, K. Tolerance and Physical Dependence in Intact and Chronic Spinal Dogs During Addiction to 10820 (4-4-Diphenyl-6-Dimethylamino-Heptanone-3), *Federation Proc* 6 384 (March) 1947

Eddy, Wilson and Moran⁸ found that if the dosage was held to the minimum required for relief of pain tolerance to the analgesic effect developed slowly, if at all, in patients with chronic painful diseases

Less is known concerning the development of habituation to methadon Schauman, quoted by Kleiderer,¹ stated that no cases of "primary" addiction to methadon had occurred in Germany Schauman also believed that the drug did not produce "true euphoria" Isbell and others⁸ saw no evidence of euphoria or of habituation after the repeated administration of small doses to patients with chronic painful diseases Kirchhof and David^{4b} noted the development of euphoria in 2 of 84 patients who received the drug for various medical conditions Wikler⁹ has observed the development of strong habituation to the drug in 1 man who was given it for several months for the relief of pain due to metastatic hypernephroma

There is little information concerning the development of physical dependence to methadon Wikler and Frank⁷ produced strong physical dependence in normal dogs, dogs with chronic spinal disease and decorticate dogs by administering four doses of the drug daily for twenty-eight to seventy days Signs of abstinence appeared sooner, were more severe and subsided somewhat more quickly after the withdrawal of methadon than after the withdrawal of morphine Woods, Wyngaarden and Seevers¹⁰ were unable to detect signs of physical dependence following withdrawal of methadon from monkeys after administration of one dose of 5 to 12 mg of methadon per kilogram of weight daily for seventy-five to ninety-six days Kirchhof and David^{4b} saw no evidence of a withdrawal syndrome in patients who had received 112.5 to 350.0 mg of methadon over periods of six to twenty days After abrupt withdrawal of methadon for twenty-four to forty-eight hours from patients who had received it for twenty to one hundred and fifty-four days or more, Isbell and others⁸ saw signs suggestive of physical dependence in 2 of 14 subjects

METHODS

Three separate types of experiments were carried out in the evaluation of the liability of addiction to methadon

1 Methadon was administered to men showing well developed signs of abstinence from morphine

2 Methadon was substituted for morphine in cases of proved addiction to the latter, followed by abrupt withdrawal of the methadon

8 Isbell, H., Wikler, A., Eddy, N. B., Wilson, J. L., and Moran, C. F. Tolerance and Addiction Liability of 6-Dimethylamino-4-4-Diphenyl-Heptanone-3 (Methadon), *J. A. M. A.* **135** 888-894 (Dec 6) 1947

9 Wikler, A. Personal communication to the authors

10 Woods, L. A., Wyngaarden, J. B., and Seevers, M. H. The Addiction Potentialities of 1,1-Diphenyl-1-(Dimethylaminoisopropyl)-Butanone-2 (Amidone) in the Monkey, *Federation Proc.* **6** 387 (March) 1947

3 Addiction to methadon was produced in former morphine addicts, who volunteered for the experiments, by the administration of four doses of the drug daily for periods varying from twenty-eight to one hundred and eighty-six days

The first two types of experiments are based on the hypothesis, which has been developed by Himmelsbach,¹¹ that a drug which will alleviate or prevent the appearance of signs of abstinence will itself produce physical dependence. Such studies are useful chiefly in studying physical dependence and in assessing the value of a new drug in the treatment of the withdrawal illness. They do not yield much information concerning habituation to the compound being tested. The rationale of the third type of experiment is obvious, and information can be gained concerning tolerance, physical dependence and habituation.

TABLE 1—*Point System for Measuring Abstinence Syndrome Intensity by the Day (D) or by the Hour (H)**

Sign	(D) By Day		(H) By Hour	
	Points	Limit	Points	Limit
Yawning	1	1	1	1
Lacrimation	1	1	1	1
Rhinorrhea	1	1	1	1
Perspiration	1	1	1	1
Mydriasis	3	3	3	3
Tremor	3	3	3	3
Gooseflesh	3	3	3	3
Anorexia (40 per cent decrease in caloric intake)	3	3		
Restlessness	5	5	5	5
Emesis (each bout)	5		5	5
Fever (for each 0.1 C [0.2 F] rise over mean addiction level)	1		1	10
Hyperpnea (for each resp./min. rise over mean addiction level)	1		1	10
Rise in morning systolic blood pressure (for each 2 mm. of mercury over mean addiction level)	1	15	1	10
Weight loss (for each pound from last day of addiction)	1			

*Total intensity of abstinence syndrome per day or per hour is the sum of the points scored in the (D) or (H) columns respectively, with due attention to the limits.

The patients were studied in a special ward devoted to clinical investigation. They were isolated from the other patients in the institution, and special precautions were taken to prevent the introduction of unauthorized drugs into the ward.

Physical examinations were made of all the subjects before they were accepted for the experiments. These were repeated at monthly intervals throughout the period of administration of drugs and daily during the withdrawal period.

Observations on rectal temperature, pulse and respiratory rates, systolic blood pressure and signs of abstinence (table 1) were made three times daily by trained

11 Himmelsbach, C. K. Clinical Studies of Drug Addiction. I. The Absence of Addiction Liability in "Perparin," Supplement 122 to the Public Health Reports, United States Treasury Department, Public Health Service, 1937, pp. 1-4.

attendants, according to the procedure outlined by Kolb and Himmelsbach¹² Total hours of sleep were determined daily All food eaten was weighed and the daily caloric intake calculated from tables of caloric values Notes on the general behavior and appearance of the men were written three times daily These observations were carried out for a seven day period (preaddiction or control period), throughout the period of administration of the drug (addiction period) and for six to fourteen days after discontinuance of the use of the drug (withdrawal period) The intensity of the abstinence syndromes observed was calculated according to the system of Himmelsbach (table 1)

The following laboratory tests were made in the preliminary week of observation and once weekly during addiction to either methadon or morphine determinations of the total red and white blood cell counts, hemoglobin contents and differential white blood cell counts, urinalyses for specific gravity, sugar, albumin and formed elements and determinations of blood bilirubin and fasting blood sugar contents and of cephalin-cholesterol flocculation Blood counts and urinalyses were carried out according to the procedures described by Kolmer and Boerner¹³ Blood bilirubin contents were determined by the technic of Malloy and Evelyn¹⁴ Blood sugar levels were estimated by the procedure of Benedict¹⁵ on Somogyi zinc filtrates¹⁶ Cephalin-cholesterol flocculation was determined according to the technic of Hanger,¹⁷ Difco antigen being used

Intravenous dextrose tolerance tests¹⁸ were carried out on 3 of the subjects who were addicted to methadon for one hundred and eighty days or more in the preliminary week of observation, once monthly during the addiction period and on the third, fourth or fifth days of withdrawal Basal metabolic rates were determined in the preaddiction period and at intervals during addiction Electrocardiograms (three standard limb leads and lead CF₄) were obtained before and at intervals during administration of the drug and after withdrawal

The effect of methadon on the pain threshold was determined by the thermal radiation method of Hardy, Wolff and Goodell¹⁹ In these experiments, two or

12 Kolb, L., and Himmelsbach, C. K. Clinical Studies of Drug Addiction III. A Critical Review of the Withdrawal Treatments with Method for Evaluating Abstinence Symptoms, Supplement 128 to the Public Health Reports, United States Treasury Department, Public Health Service, 1938, pp. 1-31

13 Kolmer, J. A., and Boerner, F. Approved Laboratory Technic, ed. 4, New York, D. Appleton-Century Company, Inc., 1945

14 Malloy, H. T., and Evelyn, K. A. The Determination of Bilirubin with the Photoelectric Colorimeter, *J. Biol. Chem.* **119**: 481-490 (July) 1937

15 Benedict, S. R. The Analysis of Whole Blood. II. The Determination of Sugar and Saccharoids (Non-Fermentable, Carbohydrate-Reducing Substances), *J. Biol. Chem.* **92**: 141-159 (June) 1931

16 Somogyi, M. A Method for the Preparation of Blood Filtrates for the Determination of Sugar, *J. Biol. Chem.* **86**: 655-663 (April) 1930

17 Hanger, F. M. Serological Differentiation of Obstructive from Hepatogenous Jaundice by Flocculation of Cephalin-Cholesterol Emulsions, *J. Clin. Investigation* **18**: 261-269 (May) 1939

18 Lozner, E. L., Winkler, A. W., Taylor, F. H. L., and Peters, J. P. The Intravenous Glucose Tolerance Test, *J. Clin. Investigation* **20**: 507-515 (Sept.) 1941

19 Hardy, J. D., Wolff, H. G., and Goodell, H. Studies on Pain. A New Method for Measuring Pain Threshold, Observations on Spatial Summation of Pain, *J. Clin. Investigation* **19**: 649-657 (July) 1940

three thresholds agreeing to within ± 5 per cent obtained prior to administration of the drug, and the thresholds were redetermined at intervals of twenty to thirty minutes for four to six hours after administration of the test dose of methadon. The intensity of the radiation at the pain threshold was measured in watts.²⁰ The results were expressed as percentage change from the predose threshold and were plotted graphically against time. Five control tests were made after the administration of 5 mg doses to 10 men prior to addiction to methadon. During the addiction period, the tests were repeated weekly. The control (predose) determinations during addiction were made at least ten hours after the last regular dose of the drug. The test doses during addiction were one fourth the total daily dose administered on the day of experiment.

Electroencephalograms were made on 14 subjects before and at various intervals during the addiction period as well as in the withdrawal phase. In 2 cases, monopolar and bipolar tracings were obtained from frontal, precentral, parietal and occipital leads. In the others only precentral and occipital monopolar and bipolar tracings were made. It was found that all the changes were adequately represented in the latter types of recording. The subject reclined on a comfortable bed in a semisoundproofed, air-cooled, electrically shielded room, and an observer ensured wakefulness with relaxation. The scalp leads were standard, and the ears, interconnected and grounded, were utilized for reference electrodes. The scalp and ear leads were connected through selector switches with the input of four resistance-capacity coupled amplifiers whose output activated four string galvanometers. Deflections were recorded photographically on moving bromide paper.

The Otis self-administering intelligence test, an arithmetic test, a perseveration test, a visual-motor coordination test and the Rorschach test were administered in the week prior to addiction and in the last week of the addiction period to all the volunteers who were addicted to methadon. The Otis test is a conventional self-administering test with a time limit of one-half hour. The arithmetic test consists of three columns of simple arithmetic problems, the first being addition, the second multiplication and the third subtraction. It is scored in terms of time for completion and number of errors. The perseveration test consists of the addition to the arithmetic test of a fourth column of problems in which subtraction, multiplication and addition occur in random order. The perseveration score is computed by subtracting the mean time required to complete the first three columns from the actual time required for the fourth column. High perseveration scores are associated with loss of mental shift, or with difficulty in changing from one type of problem to another. The coordination test involves the copying of various geometric figures from a model and is scored in terms of speed and accuracy. The Rorschach test involves the presentation to the subject of ten ink blot pictures, with instructions to look at each blot as it is presented and report what it, or any part of it, resembles. The subject's responses to the stimulus material are used to deduce his basic personality structure, including the degree and mode of control with which he tries to regulate his experience and actions, his emotional responsiveness to stimulation from without and to prompting from within, his creative and imaginative capacities and the use he makes of them and a general estimate of the degree of security or anxiety and of the relative degree of maturity in the total personality development. The Rorschach tests were scored according to a standard procedure.²¹

20 Andrews, H. L. The Effect of Opiates on the Pain Threshold in Post Addicts, *J Clin Investigation* 22 511-516 (July) 1943

The hydrochloride of racemic²² methadon²³ was the drug used in all the experiments. It was dissolved in isotonic sodium chloride solution and was administered subcutaneously.

RESULTS

Relief of Symptoms of Abstinence From Morphine by Administration of Methadon—Methadon was administered to 10 men who were showing moderate to severe signs of physical dependence thirty-two hours after the last injection of morphine. These subjects had all been stabilized on 75 to 90 mg of morphine subcutaneously four times daily for three weeks prior to the experiment. Observations on the intensity of abstinence were made hourly from the twenty-fourth to the thirty-second hour according to the procedure of Himmelsbach²⁴ and the intensity of abstinence expressed in points. The method for calculating the hourly point score is shown in table 1. After the test dose was injected, hourly observations were continued for ten hours in order to assess the effect of the drug on the course of the abstinence. The doses of methadon given varied between 12 and 30 mg (a ratio of 1 mg of methadon for each 3 to 6 mg of the stabilization dose of morphine). The average dose given was 21 mg, and the average ratio was 1 mg of methadon for each 4 mg of the stabilization dose of morphine.

In all instances the intensity of symptoms of abstinence was reduced after injection of the methadon (fig 1). The larger the dose given, the greater was the degree of relief from the withdrawal symptoms. The reduction in the intensity of symptoms of abstinence was as good as that seen after the administration of 30 mg of morphine to 4 of the same subjects under similar conditions, and it persisted longer. When 1 mg of methadon or more was given for each 4 mg of the stabilization dose of morphine, the reduction in the intensity of symptoms of abstinence persisted throughout the ten hour period of observation following the test dose. When the ratio was 1 mg of methadon for each 5 or more mg of the stabilization dose of morphine, the degree of relief from the withdrawal symptoms was less and the intensity of signs of abstinence began to increase eight hours after the test injection.

21 Klopfer, B, and Kelley, D M. *The Rorschach Technique. A Manual for a Projective Method of Personality Diagnosis*, ed 1, Yonkers-on-Hudson, New York, World Book Company, 1942.

22 Methadon is an optically active compound, with both dextrorotatory and levorotatory stereoisomers. These isomers have been separated, and it has been determined that the levoroatary compound carries nearly all the analgesic activity.

23 Supplied through the courtesy of Dr K. K. Chen, Eli Lilly & Company, Indianapolis, Ind.

24 Himmelsbach, C K. Studies of Certain Addiction Characteristics of Dihydromorphine ("Paramorphan"), Dihydrodesoxymorphine-D ("Desomorphine"), Dihydrodesoxycodine-D ("Desocodine"), and Methyl dihydromorphine ("Metopon"), *J Pharmacol & Exper Therap* 67:239-249 (Oct) 1939.

In 7 other cases, in which stabilization doses of 60 to 180 mg of morphine had been given four times daily, 1 mg of methadon was administered for each 4 mg of the stabilization dose at the thirty-sixth hour of abstinence. The dose was repeated to the thirty-eighth hour. By the fortieth hour all evidence of abstinence had disappeared, and point scores had fallen below 10.

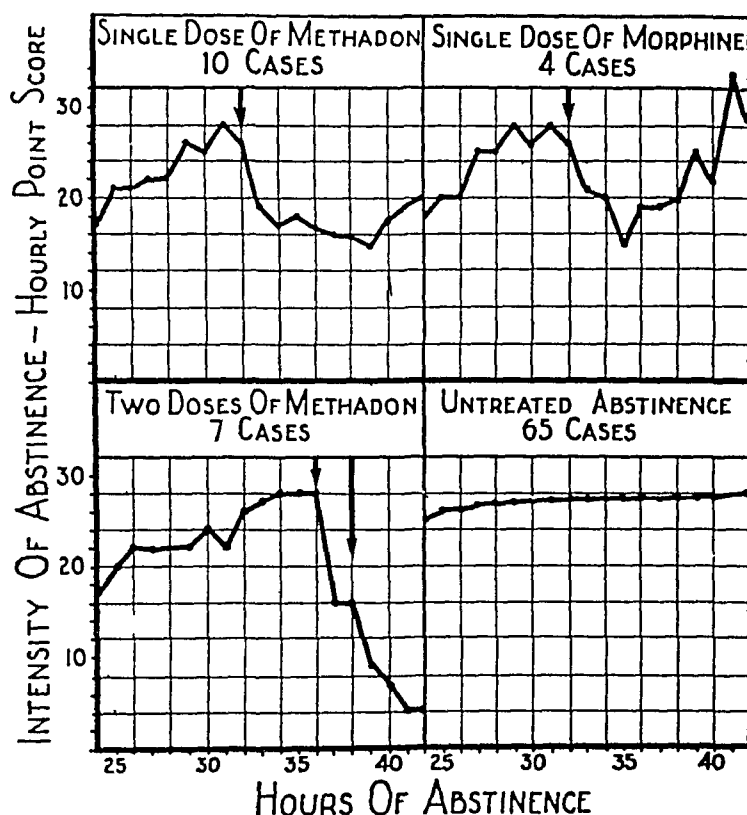


Fig 1—Relief of symptoms of abstinence from morphine by administration of methadon. The intensity of abstinence is expressed in hourly points^{27a}. At the upper left are average point scores of 10 subjects who received 21 mg of methadon at the thirty-second hour of abstinence. Arrows indicate injection of drug. Note prompt decline in the intensity of abstinence syndrome and the prolonged effect. At the upper right are average point scores of 4 of the same subjects who received 30 mg of morphine at the thirty-second hour of a subsequent abstinence. Note decline in the intensity of abstinence followed by a return to the original level at about the seventh hour after the injections. At the lower left are average point scores of 7 subjects who received methadon at the thirty-sixth and thirty-eighth hours of abstinence. Note almost complete abolition of symptoms of abstinence four hours after the second dose. At the lower right is shown the course of untreated symptoms of abstinence from morphine based on 65 control cases of Himmelsbach.

SUBSTITUTION OF METHADON FOR MORPHINE

Methadon was substituted for morphine in 12 cases. The intensity of physical dependence was determined in all 12 instances by a preliminary thirty-six hour withdrawal of morphine. The daily point score system of Himmelsbach (table 1) was used in assessing the degree of physical de-

pendence The least amount of morphine which would just prevent the appearance of withdrawal phenomena (the stabilization dose) in these patients varied between 60 and 180 mg of morphine four times daily After the preliminary withdrawal, 9 of the 12 men were given morphine again for seven to fourteen days, after which methadon was substituted for morphine at a ratio of 1 mg of methadon for each 4 to 5 mg of the stabilization dose of morphine The administration of methadon was continued for fourteen days after the substitution was effected In the remaining 3 cases methadon was administered at the height of abstinence and the effect on the withdrawal symptoms observed, after which administration of the drug was continued for twenty-one days

When 1 mg of methadon was substituted for each 4 mg of morphine, no signs of abstinence appeared and the change was not noticed by the patients When 1 mg of methadon was substituted for each 5 mg of morphine, the patients became irritable and minor signs of physical dependence (rhinorrhea, elevation of systolic blood pressure and slight fever) appeared These signs could be abolished by increasing the dose of methadon

A considerable degree of cross-tolerance was noted between methadon and morphine in these substitutions Forty-five milligram doses of methadon, which resulted in sedation in nontolerant subjects, had little effect other than the suppression of signs of physical dependence on the men who were tolerant to 180 mg doses of morphine

After methadon had been substituted for morphine, an attempt was made in 3 cases to determine the dosage of methadon which would just prevent the appearance of signs of abstinence (stabilization dose) The amount of methadon was reduced progressively over a period of five days No signs of abstinence appeared, so that a stabilization dose could not be determined The reduction in dosage was stopped when a level of 1 mg of methadon for each 12 mg of morphine had been reached, and the dosage was maintained at the level for seven days prior to withdrawal

Observations were carried out on the subjects for fourteen days after abrupt withdrawal of methadon In all instances a definite abstinence syndrome developed which was slower in onset and much less intense than that seen after the withdrawal of morphine

The patients had no subjective complaints during the first forty-eight hours of abstinence They stated that they felt well, but all reported that they could still notice the effects of the drug On the third day they began to complain of weakness, anxiety, anorexia, vague abdominal discomfort, sweating and "hot and cold flashes" These complaints reached maximum intensity on the sixth day of abstinence and

had largely subsided by the tenth day. After the third day of abstinence the men appeared tired and weak but never so miserable as after the abrupt withdrawal of morphine. They tried various schemes in efforts to persuade the physician to give them either methadon or morphine but were able to maintain their emotional control when their requests for drugs were refused.²⁵ Ten of the 12 men felt that the symptoms of abstinence following the withdrawal of methadon were much milder than those after withdrawal of morphine, but all agreed that they were sufficiently intense to cause them to return to the use of morphine or methadon if either drug had been obtainable.

Objectively, few signs of disturbed autonomic function were seen. The incidence of these signs is compared in table 2 with the incidence found during the preliminary test withdrawal of morphine. The few autonomic signs which were observed were not consistently present in the same person. Vomiting occurred infrequently, and diarrhea was never observed.

Despite the low incidence of signs of autonomic dysfunction, definite evidence of a withdrawal illness was detected in the measurable signs of abstinence (table 3). The rectal temperature, systolic blood pressure and pulse and respiratory rates became elevated above both the preaddiction and addiction levels. Body weight decreased slightly, as did hours of sleep. None of these changes were as severe as those seen after the withdrawal of morphine.

The average daily Himmelsbach point score (intensity of abstinence syndrome) rose slowly and reached a maximum of 25 points on the sixth day. Such a point score, while significant, is indicative of a degree of abstinence syndrome which should in ordinary practice require little treatment with morphine or with morphine-like drugs.

DIRECT ADDITION TO METHADON

Methadon was administered to 15 subjects who volunteered for the experiment. These men were veteran morphine addicts who were serv-

²⁵ Experience with abrupt withdrawal of methadon after substitution for morphine in other wards of the hospital has not been as satisfactory as in the research ward. Although the abstinence syndromes seen after withdrawal of methadon were mild, 9 of 11 patients treated outside of the research ward created various disturbances in efforts to obtain drugs. One man cut his wrists, another threatened suicide and 7 would not permit observation to be made. (Dr. Herbert Wieder supplied these data.) However, if the dosage of methadon is reduced over the course of seven to ten days after substitution for morphine, not only are few signs of abstinence observed but loss of emotional control seldom occurs. The majority of experienced morphine addicts have expressed decided preference for reduction of morphine addiction with methadon rather than reduction with morphine.

ing sentences for violation of the Harrison Narcotic Act They had all been abstinent from opiates for at least three months prior to the experiment Their ages varied between 22 and 48 years They had no significant physical defects Thirteen of the subjects were classified as pleasure-seeking psychopaths Two were homosexuals

The initial dosage in all cases was 20 mg of methadon daily This level was maintained for a week, and thereafter the dosage was increased as rapidly as tolerance permitted The total daily dosage was divided into four equal doses which were administered at 6 a m, 10 a m, 4 p m, and 10 p m

TABLE 2—*Nonmeasurable Signs of Abstinence After Withdrawal of Methadon Substituted for Morphine*

Sign	Abstinence From Morphine*		Abstinence From Methadon After Substitution for Morphine and Stabilization for Fourteen to Twenty-One Days*													
	Day		Day of Abstinence													
	1	1½	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Yawning	12	12	3	4	5	4	2	6	2	2	2	1	1	1	1	0
Lacrimation	10	12	0	3	1	1	0	1	0	0	0	0	0	1	0	0
Rhinorrhea	6	9	1	2	0	0	0	0	1	0	0	0	0	1	0	0
Perspiration	4	8	1	2	1	0	0	0	0	0	0	0	0	0	0	0
Gooseflesh	3	8	1	0	0	0	0	1	0	0	0	0	0	0	0	0
Mydriasis	10	12	2	3	3	1	0	0	0	0	0	1	0	0	1	0
Tremor	0	5	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Restlessness	0	8	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Emesis (total no of bouts)	6	24	0	0	2	1	0	0	0	0	0	0	0	0	1	0
Diarrhea	0	7	0	0	0	0	0	0	0	0	0	0	0	0	0	0

*Figures represent the number of a total of 12 subjects who exhibited the sign on the day noted except for emesis for which the total number of bouts observed in 12 patients is recorded Under "abstinence from morphine" the incidence of signs observed in a preliminary thirty-six hour withdrawal from morphine prior to substitution and stabilization on methadon is recorded

Three of the men received the drug for twenty-eight days until they were receiving maximum dosage levels of 240 mg daily, 7 received it for fifty-six days until dosage levels of 180 mg daily were reached and 5 received it for one hundred and forty-two to one hundred and eighty-six days until the dosage level was 200 to 400 mg daily At one point in the experiment 2 of the subjects in the last group were receiving 600 to 800 mg of the drug daily Because of the appearance of signs of toxicity, the dosage was reduced to 200 to 400 mg and maintained at that level for the last sixty days of the experiment

GENERAL BEHAVIOR DURING ADDICTION

No changes were noted in the general behavior of the subjects during the first week when they were receiving only 20 mg of methadon

TABLE 3—Measurable Signs of Abstinence After Withdrawal of Methadon Substituted for Morphine

Sign	Abstinence From Morphine*		Abstinence From Methadon After Substitution for Morphine and Stabilization for Fourteen to Twenty-One Days†												Day of Abstinence			
	Day																	
	1	1½	1	2	3	4	5	6	7	8	9	10	11	12	13	14		
Rectal temperature, elevation above addiction mean	0 3C (0 51F)	0 6C (1 08F)	0 08C (0 51F)	0 1C (0 19F)	0 2C (0 36F)	0 2C (0 30F)	0 3C (0 54F)	0 25C (0 19F)	0 3C (0 51F)	0 3C (0 54F)	0 25C (0 19F)	0 2C (0 36F)	0 15C (0 27F)	0 1C (0 19F)	0 15C (0 27F)	0 05C (0 09F)		
Morning systolic blood pressure, elevation above addiction mean (millimeters of mercury)	11	28	2	3	14	10	13	11	16	11	11	12	8	7	8	6		
Respiratory rate, increase per minute above addiction mean	2	4	1	2	3	3	5	5	5	6	8	7	5	6	5	2		
Caloric intake in percentage of addiction mean	23	10	85	72	59	108	76	78	85	79	94	101	93	95	101	98		
Decrease in body weight (per cent)	0	3 3	0	0 8	1 9	1 9	1 5	1 8	1 5	1 4	1 3	0 5	0 7	0 4	0 0	0 0		
Hours of sleep	8 7	3 4	8 7	9 8	7 7	6 5	5 5	7 4	7 7	6 3	7 6	6 5	6 3	6 9	6 9	6 3		
Average daily point score	21	51	5	10	16	16	21	23	21	21	18	15	15	12	12	8		

*Figures represent the average values for all 12 men. The figures under "abstinence from morphine" represent the values found in a preliminary thirty-six hour period of abstinence from morphine prior to substitution of methadon.

daily, and they complained that the drug did not produce the desired degree of euphoria. When the dosage was increased to 40 to 60 mg daily in the second week of addiction, definite evidence of sedation appeared after the third or fourth injection, and the men began to express satisfaction with the effects of the drug. Their behavior became strikingly similar to that seen during addiction to morphine. They became less active and ceased nearly all productive work. They spent a great deal of time in bed in a dreamy state characterized by alternating periods of somnolence and wakefulness which they termed being "on the nod" or "coasting." At times they would fall asleep and burn themselves or their beds with cigarettes. They neglected their personal appearance, did not shave as frequently as they did before receiving the drug, lounged around in pajamas and did not keep their rooms tidy. When they were maintained on a given dosage level for two weeks or more, evidence of tolerance to the sedative effects would appear. The men would become more alert and would stay awake and begin to play cards or work. They usually requested increases in the dosage as soon as evidence of tolerance appeared. After each increase in dosage, evidence of sedation would reappear after the third or fourth injection of the larger doses, and the cycle would be repeated. When asleep, the patients would exhibit twitching and jerking movements and at times would carry on purposeful movements with their hands. When awakened from sleep, they would be startled. Several of them apparently had hypnagogic delusions and would hear voices just as they were about to fall asleep. Five of the 15 subjects became more irritable with each other and with the attendants as the experiment progressed.

The degree of somnolence and of lack of activity was greater than that seen during morphine addiction. The men complained about this, and said that while addicted to methadon they could do little except stay in bed. They stated that methadon lacked a peculiar quality possessed by morphine, which was termed "drive" and which they defined as a sense of ambition to work and play games. When it was pointed out that their behavior while addicted to morphine was inconsistent with these sensations, the patients were puzzled and stated that when they were receiving morphine they at least felt ambitious but when receiving methadon they knew that they were lazy.

PSYCHOLOGIC OBSERVATIONS DURING ADDICTION

The average results of the Otis, arithmetic, coordination and perseveration tests are shown in table 4. As measured by the Otis test, the intelligence quotient (I Q) was lowered 6.8 points in the week prior to withdrawal, as compared with that in the week prior to addiction. The arithmetic test was performed at almost the same rate of speed,

but there were more errors. Visual-motor coordination and perseveration tests were performed at somewhat higher rates of speed, but with considerably more errors. The greater rapidity of visual-motor response and the increased fluidity of shift appear to be vitiated by greater inaccuracy. A decrease in the efficiency of intellectual functioning was indicated.

The subjects used in this study appeared to be diverse in personality structure as measured by the Rorschach method. However, in every case there were changes in response to the tests administered prior to and during addiction. These changes may be said to fall into two general categories:

Those subjects whose primary difficulty appeared to involve inhibition conflicts in relation to the expression of their instinctual drives showed during addiction a decrease in the guilt and anxiety associated

TABLE 4—*Effects of Addiction to Methadon on Psychologic Measurements*

	Week Prior to Addiction	Week Prior to Withdrawal
Otis intelligence quotient	97	90
Arithmetic		
Time	109.8	109.6
Errors	1.5	2.0
Coordination		
Time	295.9	270.7
Errors	2.0	3.6
Perseveration		
Time	21.5	17.7
Errors	2.3	4.0

with these conflicts, accompanied either with increased sensuality, immaturity and egocentricity or with decreased accessibility to affective stimulation. When test records of the same subjects were compared while they were given morphine sulfate and while they were given methadon, the first result occurred most often with methadon while the second most often accompanied the use of morphine.

A second group, whose original records suggested that they were relatively free from anxiety but were egocentric, self centered and emotionally withdrawn, revealed a greater accessibility to affective stimulation during addiction. When test records of subjects in this group were compared while they were given morphine sulfate and while they were given methadon, results were similar for both drugs.

CLINICAL OBSERVATIONS DURING ADDICTION

The average changes in temperature, pulse, respiratory rates, blood pressure, body weight, caloric intake and sleep are represented in figure 2, which shows the average data obtained in the first and last weeks of addiction on the 5 men who received the drug for one hundred and forty-two to one hundred and fifty-six days

Rectal temperature was decreased about 0.5 C (0.9 F) in the first days of addiction, gradually rose to the preaddiction level and after the

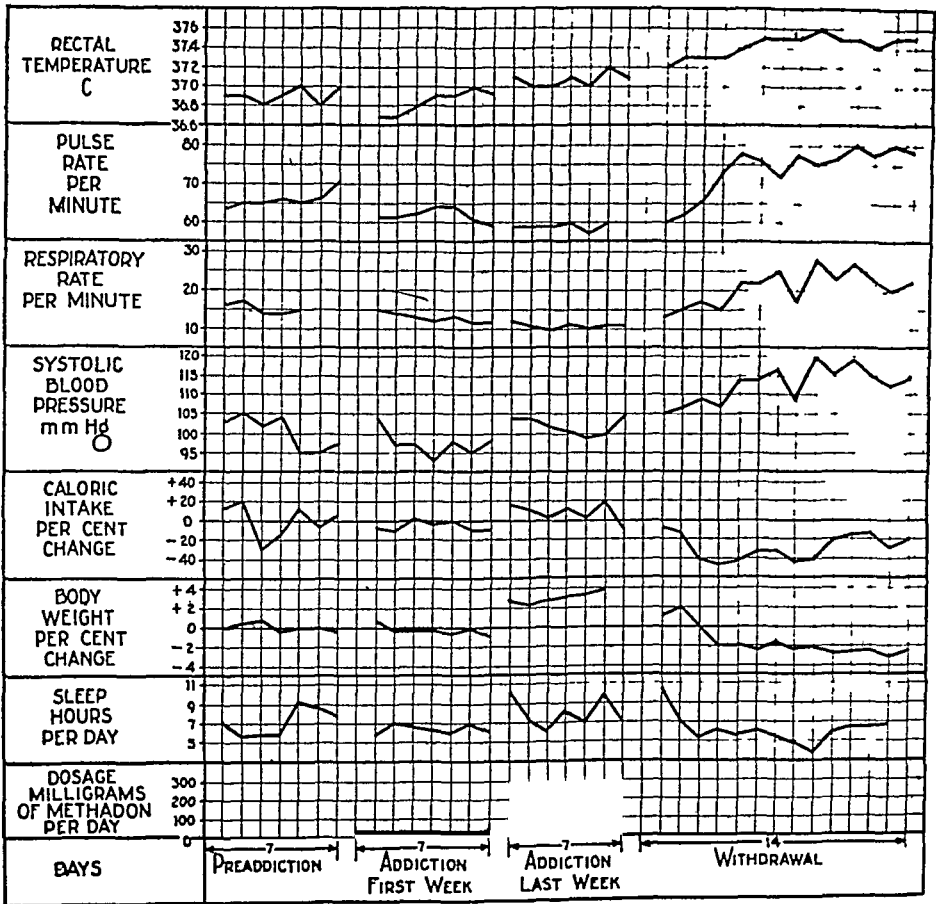


Fig 2—Average of clinical observations on 5 subjects during addiction to methadon for four and a half to six months. Only the observations made in the first and last weeks of addiction are recorded. Note especially the changes following withdrawal.

first week remained at 0.2 to 0.4 C (0.36 to 0.7 F) above the preaddiction level. The pulse rate was slowed about 10 beats per minute during most of the period of addiction. The respiratory rate was depressed an average of 4 beats per minute. The morning systolic blood pressure was 6 to 10 mm lower during the first four months of addiction than during the control period, but it was increased slightly above

the control level in the fifth and sixth months of addiction. Caloric intake declined in the first two weeks of addiction but was normal or increased thereafter. The men lost weight early in the experiment, but subjects who received the drug for four and a half to six months regained the lost weight and at the end of the addiction period weighed more than before they became addicted. Sleep was little affected, although, as noted previously, all subjects spent a great deal of time in bed in a semisomnolent state.

One subject was nauseated throughout the first two weeks of addiction and ate little. As he became tolerant, the nausea ceased and his caloric intake became normal. After the first week all the men were severely constipated and resorted to cathartics and enemas. No tolerance developed to the constipating action of the drug. Some men complained of difficulty in initiating urination during the first two weeks of addiction but thereafter had no complaints referable to the urinary tract.

No generalized dermatitis attributable to methadon developed in any of the patients. In all subjects, however, the skin over the sites of injection became reddened, thickened and indurated. The induration became noticeable when the dose reached 25 mg four times daily. The larger the dose, the more severe was the reaction. With doses to 100 mg or more, blebs and bullae developed over the injection sites, and serum would ooze from the needle punctures for several hours after administration of a dose. Hypesthesia developed over these areas. None of the hardened areas became infected or necrotic. After withdrawal of the drugs, the inflammation and induration of the skin gradually decreased. Some induration was still noticeable six months after the last dose had been administered to the men who received the largest doses.

Miosis was easily detected in the first week of addiction to methadon but was never so marked as during addiction to morphine. After the first week the size of the pupils appeared to be normal. Methadon differs from morphine in this respect, as tolerance to the pupil-constricting action of morphine does not seem to occur.

A typical facies developed in all the subjects after they were receiving a dosage level of 100 mg or more of methadon daily. They exhibited facial pallor and a peculiar staring expression which appeared to be due to a reduction in the rate of blinking. The facies, lethargy, twitching and jerking while asleep and the increased startle response on awakening constitute a clinical picture which is characteristic of chronic methadon intoxication.

TOLERANCE TO THE ANALGESIC EFFECT

Tolerance to the pain-threshold-elevating action of the drug developed rapidly in the 10 subjects who received it for twenty-eight to

fifty-six days The patients were completely tolerant to this action of methadon after administration of 5 mg four times daily for seven days When tolerance had been developed to any given dosage level, an increase in the dosage was followed by elevation of the pain threshold On continuation of the increased dosage, tolerance to the new level would develop After administration of the drug for fifty-six days, 7 of the

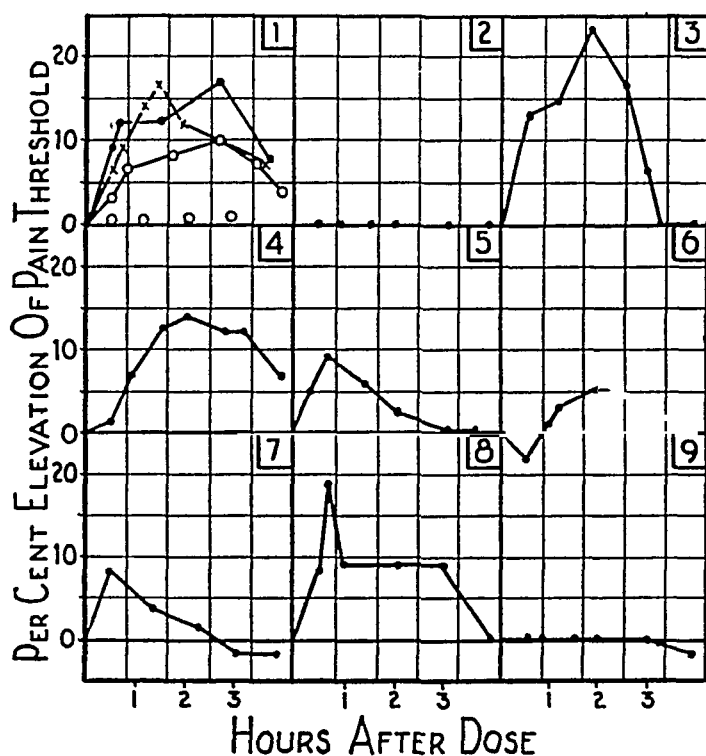


Fig 3—Development of tolerance to the pain threshold-elevating action of methadon in subject 729 Curve 1, solid circles indicate greatest response to a 5 mg dose of methadon prior to addiction, open circles smallest response to a 5 mg dose, crosses average response to a 5 mg dose and open circles with dots control after injection of distilled water Curve 2, response to a 5 mg dose after seven days of addiction Curve 3, response to a 15 mg dose on the eighth day of addiction Curve 4, response to a 15 mg dose after fourteen days of addiction Curve 5, response to a 15 mg dose after twenty-one days of addiction Curve 6, response to a 25 mg dose after twenty-eight days of addiction Curve 7, response to a 30 mg dose after thirty-five days of addiction Curve 8, response to a 45 mg dose after forty-two days of addiction Curve 9, response to a 45 mg dose after fifty-six days of addiction

men were almost completely tolerant to the paint-threshold-elevating action of 45 mg doses The development of tolerance in 1 of these subjects is shown in figure 3

LABORATORY OBSERVATIONS DURING ADDICTION

No significant changes were observed during the addiction period in blood bilirubin levels, cephalin-cholesterol flocculation, nonprotein

nitrogen levels, basal metabolic rates or results of urinalyses. The only change seen in the electrocardiogram was the development of sinus bradycardia without increase in the P-R interval.

Red blood cell counts and hemoglobin levels were unaltered in the subjects who received the drug for twenty-eight to fifty-six days. After administration of methadon for three months, a mild normocytic and normochromic anemia developed in all the 5 men who took the drug for one hundred and forty-two to one hundred and eighty-six days. The red blood cell counts fell from preaddiction levels of 4,600,000 to 5,200,000 to levels of 3,760,000 to 4,250,000 during addiction. Hemoglobin levels declined 2.5 to 3.0 Gm per hundred cubic centimeters. After the development of the anemia, the dosage of methadon was reduced from between 400 and 600 mg daily to between 200 and 400 mg, and thereafter red blood cell counts and hemoglobin values remained stationary. No consistent changes were noted in total differential white blood

TABLE 5—*Average Fasting Blood Sugar Content During Addiction to Methadon*

Subject	Pread-diction	Month of Addiction					
		1	2	3	4	5	6
744	68	78	77	75	74	75	74
745	62	57	61	58	54	51	59
742	68	67	67	62	61	61	63

*Figures represent the average of four to ten determinations in the periods shown.

cell counts during addiction. The fasting blood sugar contents in the 10 subjects who received the drug for twenty-eight to fifty-six days tended to be in the low normal range during addiction.

The blood sugar contents in 3 of the men who received methadon for one hundred and eighty to one hundred and eighty-six days were studied intensively. The effect of the drug on intravenous dextrose tolerance curves was more striking than the effect on fasting blood sugar. Average fasting blood sugar contents tended to be lower during addiction than during the control period in 2 of the subjects (table 5). The average fasting blood sugar level of the third subject was slightly raised throughout the period of addiction. In all 3 subjects intravenous dextrose tolerance curves were lower during addiction than during the control period. The maximum lowering of the tolerance curves was noted during the fifth month of addiction. The tolerance curve obtained on subject 745 during the fifth month of addiction is shown in figure 4.

CHANGES IN THE ELECTROENCEPHALOGRAM DURING ADDICTION

In all cases the electroencephalographic changes were qualitatively the same and may be summarized as follows. During continued administration of methadon there was a progressive shift to the slow side of the

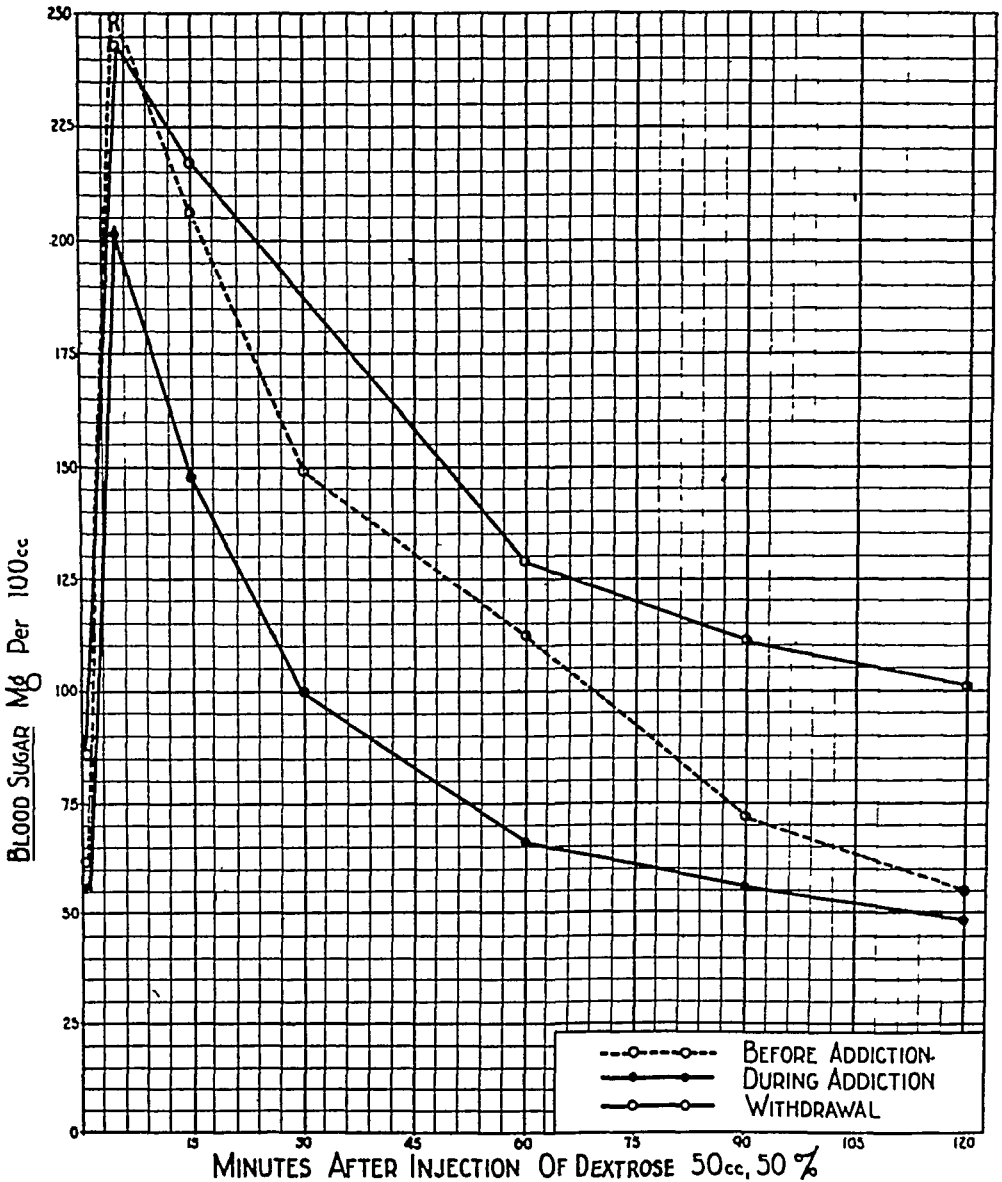


Fig. 4—Intravenous glucose tolerance curves on subject 745. The curve shown during addiction was obtained during the fifth month. The withdrawal curve was obtained on the fifth day of abstinence.

frequency spectrum. In all cases in which control records showed a dominant alpha rhythm the percentage of time during which the latter was present (alpha percentage) decreased and the mean alpha frequency became slower, delta activity (4 to 6 per second) appeared and later dom-

inated the record. In subject 734 alpha activity in the control record was scant, normal beta rhythms predominating. During addiction, beta waves disappeared and were replaced by slower alpha frequencies. The dosage levels at which first definite evidence of slowing occurred varied greatly, ranging from 5 mg to 45 mg four times daily.

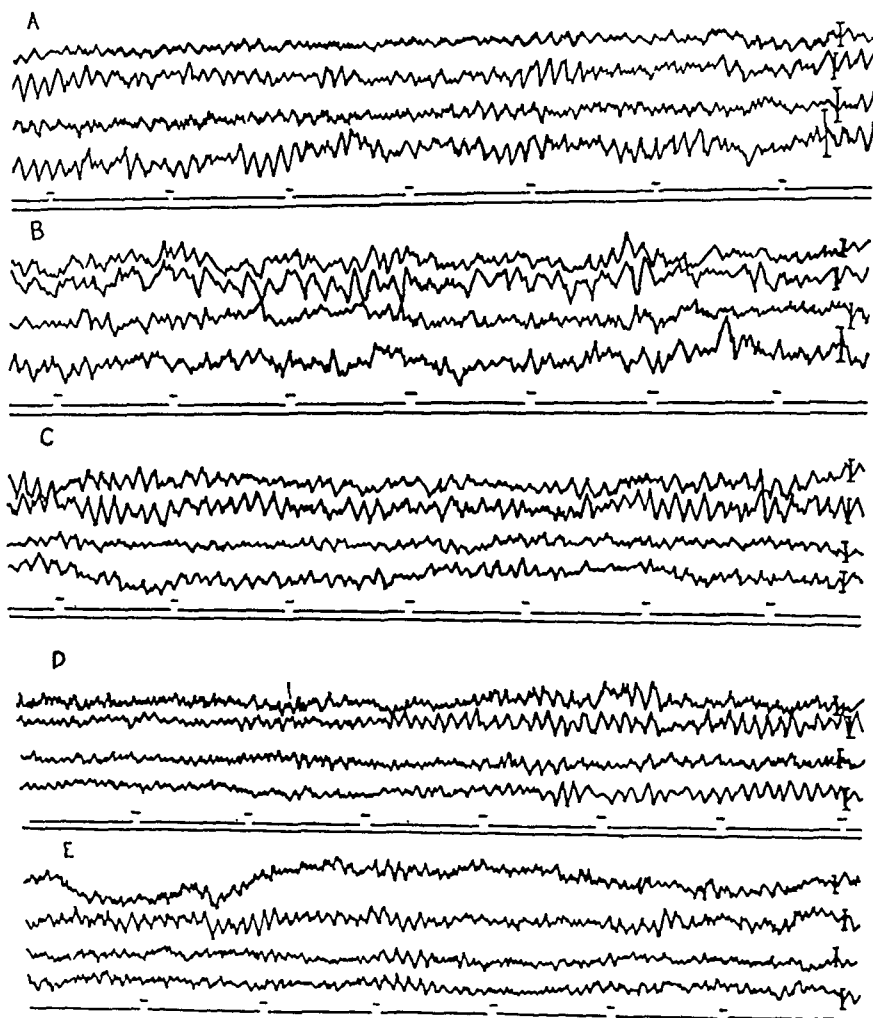


Fig 5—Tracings of electroencephalograms during one hundred and seventy-six days of continued administration of methadon in subject 744. In all records, the uppermost tracing is left precentral monopolar, followed in order by right occipital monopolar, precentral bipolar and occipital bipolar. The time is in seconds and the calibrations 25 microvolts. *A*, control (preaddiction), the record is normal, with a mean alpha frequency of 9.1 cycles per second. *B*, one hundred and nineteenth day, the dose level is 65 mg four times daily and the total amount administered 10.75 Gm. Note marked slowing of pattern, with little alpha activity and predominance of 4 to 6 cycles per second rhythms of moderate amplitude, most prominent in the occipital monopolar tracing. *C*, one hundred and sixty-eighth day, the dose level is the same, with a total of 23.50 Gm. Note tolerance indicated by practical disappearance of 4 to 6 cycles per second activity and predominance of alpha rhythms, the mean frequency of which is 8.7 cycles per second. *D* is a record made at the thirty-sixth hour and *E* one made at the seventh day of abstinence. Both records are normal and comparable to *A*, although the mean alpha frequencies are higher (9.4 and 9.9 cycles per second) than the control value.

In 10 of the 14 cases definite evidence of tolerance was shown by a partial shift of the frequency spectrum toward the faster side, although the records revealed abnormal slowness throughout the addiction period (fig 5)

CHANGES FOLLOWING WITHDRAWAL OF METHADON

Withdrawal of methadon was abrupt and complete in all cases. Observations were carried out for only six days on the 10 men who received the drug for twenty-eight to fifty-six days. The six day period of observation was based on experience with the morphine abstinence syndrome and is sufficiently long for evaluating the withdrawal sickness after discontinuance of the use of morphine. However, because of the continuation of complaints by these 10 subjects, who were the first from whom methadon was withheld, after discharge from the research ward, the observation period was extended to fourteen days for the 5 men who were given doses producing addiction for four and a half to six months.

After withdrawal, a definite abstinence syndrome ensued in all 15 cases. The manifestations of this syndrome, though milder than those seen after the withdrawal of morphine, were consistently observed in all men and at the same time. Subjectively, the men made no complaints in the first two days of abstinence and said that they were still under the influence of the drug (were "loaded"). On the third day of abstinence they began to complain of anxiety, insomnia, vague gastric distress, headache and, occasionally, tinnitus. The men did not suffer from the muscle aches and cramps which are so troublesome after the withdrawal of morphine. The subjective symptoms increased in intensity until the sixth day of abstinence, after which they gradually declined. Some patients continued to complain of weakness for sixty days after withdrawal. Thirteen of the 15 subjects considered the subjective symptoms less severe than those following the abrupt withdrawal of morphine, but all agreed that the symptoms were sufficiently severe to cause them to return to the use of the drug had it been obtainable. Nearly all complained bitterly about the slowness in improvement. A typical comment on the tenth day of abstinence was "This stuff seems like it never will turn a man loose. When I stop a morphine habit I start getting better on the third day and keep getting better every day after that. I didn't start to get sick until the third day off, and I'm still half sick all the time and not getting better. If I were on the street I'd have a shot within five minutes."

The general appearance and behavior of 14 of the men were not greatly altered. They appeared to be tired and mildly irritable. They made frequent requests for either methadon or morphine after the third day of abstinence but did not lose emotional control when their requests were refused.

The behavior of the remaining patient, who was homosexual, was different. He had no complaints for two days, but on the morning of the third day was found in bed crying and weeping. He stated that he was not suffering from any severe symptoms of abstinence but that he was afraid that other fearful things were going to happen. He was examined by two psychiatrists, who concurred in the opinion that he was suffering from an acute anxiety state (homosexual panic) and that his condition was not due to withdrawal of the drug. This man did not regain emotional control until six weeks after withdrawal of the drug.

The outstanding feature, objectively, was the paucity of the signs of autonomic dysfunction, which are so prominent after the withdrawal of

TABLE 6—*Nonmeasurable Signs of Abstinence Following Withdrawal of Methadon After Administration for 28 to 56 Days*

Sign	Day of Abstinence*					
	1	2	3	4	5	6
Yawning	0	0	0	3	0	1
Lacrimation	0	0	1	0	0	0
Rhinorrhea	0	0	0	0	0	0
Perspiration	0	0	0	0	0	0
Gooseflesh	0	0	0	0	0	0
Mydriasis	2	1	2	1	1	3
Restlessness	0	0	0	0	0	0
Tremor	0	0	0	0	0	0
Emesis, total number of bouts	0	0	1	0	0	2
Diarrhea	0	0	0	0	0	0

*The figures represent the number of a total of 10 patients who exhibited the sign on the day noted, except for emesis, for which the total number of bouts observed in all 10 patients is recorded.

morphine. The incidence of these signs is recorded in tables 6 and 7 and should be compared with the incidence seen after withdrawal of morphine (table 8) in 19 men who were readicted to 80 mg of morphine daily for twenty-eight days (a mild morphine habit). Such signs as were observed were not constantly present in the same individual. Vomiting and restlessness were seldom observed. Diarrhea was never noted.

As was the case after substitution of methadon for morphine, the best evidence of physical dependence was obtained from the measurable signs of abstinence which are recorded in tables 9 and 10. These tables should be compared with table 11, which shows changes in the measurable signs after withdrawal of morphine. Average rectal temperatures, pulse rates, respiratory rates and systolic blood pressures were increased above pre-addiction and addiction mean levels (tables 9 and 10, fig 3). Caloric intake, hours of sleep and body weight were decreased. The changes were

less pronounced than those seen after the withdrawal of morphine and were slower in onset and longer sustained. Temperatures, pulse rates and respiratory rates had not returned to preaddiction levels even after fourteen days of abstinence.

TABLE 7—*Nonmeasurable Signs of Abstinence From Methadon After Administration for 142 to 186 Days*

Sign	Day of Abstinence													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Yawning	0	0	1	2	2	3	2	1	0	2	0	0	0	0
Lacrimation	0	0	1	1	0	0	1	0	0	0	0	0	0	0
Rhinorrhea	0	0	0	0	1	0	0	0	0	0	0	0	0	0
Perspiration	0	4	0	2	1	0	0	0	0	1	0	0	0	0
Gooseflesh	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Mydriasis	0	0	2	0	1	2	0	0	0	0	0	0	0	0
Tremor	0	0	0	0	0	0	0	0	0	0	0	0	0	0
Restlessness	0	1	0	2	0	0	2	0	3	4	0	0	0	0
Emesis, (total no of bouts)	0	1	1	1	1	0	0	0	0	0	0	0	0	0
Diarrhea	0	0	0	0	0	0	0	0	0	0	0	0	0	0

Figures represent number of a total of 5 subjects who exhibited the sign on the day noted, except for emesis, for which the total number of bouts observed in 5 patients is recorded.

TABLE 8—*Nonmeasurable Signs of Abstinence Following Withdrawal of Morphine After 28 Days of Addiction to 80 Milligrams Daily*

Sign	Day of Abstinence*					
	1	2	3	4	5	6
Yawning	17	18	8	7	4	2
Lacrimation	14	14	7	4	2	0
Rhinorrhea	13	11	4	0	0	0
Perspiration	6	1	0	0	0	0
Gooseflesh	3	6	0	0	0	0
Mydriasis	19	19	18	14	10	7
Tremor	1	0	0	0	0	0
Restlessness	1	7	6	4	2	0
Emesis, total number of bouts	9	13	1	0	1	1
Diarrhea	1	3	2	1	0	0

*The figures represent the number of a total of 19 who exhibited the sign of the day noted.

There was no consistent alteration in red or white blood cell counts after withdrawal of methadon.

Thirty-two hours after withdrawal of methadon there was no appreciable change in the fasting blood sugar content in 3 of the subjects who

received the drug for one hundred and eighty days. It is usually increased about 20 mg per hundred cubic centimeters thirty-two hours after the withdrawal of morphine. In the subsequent twelve days of withdrawal significant increases in fasting blood sugar content were observed in all 3 subjects, but the increases were not consistent and were often preceded and followed by normal levels. Glucose tolerances after withdrawal started at higher levels than during the preaddiction and addiction periods and were maintained at those levels (fig 4).

Electroencephalograms showed abnormal slowness for at least two days after withdrawal, and in 2 cases the slowing persisted for at least five days (fig 6) before a normal pattern returned.

TABLE 9—*Measurable Signs of Abstinence Following Withdrawal of Methadon After 28 to 56 Days of Addiction*

Sign	Day of Abstinence ^a					
	1	2	3	4	5	6
Rectal temperature, elevation above addiction mean	0 05C (0 09F)	0 0C	0 1C (0 19F)	0 1C (0 19F)	0 2C (0 36F)	0 25C (0 49F)
Morning systolic blood pressure elevation above addiction mean (millimeters of mercury)	3	3	8	9	8	13
Respiratory rate, increase per minute above addiction mean	1	1	3	4	3	5
Caloric intake, per cent of addiction mean	95	70	65	70	50	70
Decrease in body weight (per cent)	0	1	2	3	3	3
Hours of sleep	7 2	7 5	8 1	6 4	6 8	6 2
Average daily point score	4	6	13	14	14	20

*The figures represent average values on 10 subjects

The average intensity of symptoms of abstinence as measured by the Himmelsbach daily point score (table 1) rose slowly and did not exceed 20 (the level of significance) until the fifth or sixth day of withdrawal, at which time observations were discontinued on the group which received the drug for twenty-eight to fifty-six days. The point score continued to rise in the group which received the drug for one hundred and forty-two to one hundred and eighty-six days and reached a maximum of 33 on the ninth day of abstinence. The point score was 23 on the fourteenth day of the 5 men. These point scores, while significant, are indicative of symptoms of abstinence of such mild grade that they require little treatment. They should be compared with the scores of 50 to 60 points seen in the second and third days of withdrawal of morphine from persons strongly addicted to that drug.

TABLE 10—*Measurable Signs of Abstinence From Methadon After 142 to 186 Days of Addiction*

Sign	Day of Abstinence*													
	1	2	3	4	5	6	7	8	9	10	11	12	13	14
Rectal temperature, elevation above addiction mean	0 1C (0 19F)	0 2C (0 36F)	0 2C (0 36F)	0 2C (0 36F)	0 3C (0 51F)	0 4C (0 72F)	0 4C (0 72F)	0 4C (0 72F)	0 5C (0 9F)	0 4C (0 72F)	0 4C (0 72F)	0 3C (0 54F)	0 4C (0 72F)	0 4C (0 72F)
Morning systolic blood pressure, elevation above addiction mean	2	4	6	4	11	11	14	6	17	12	16	12	9	11
Respiratory rate, increase per minute above addiction mean	2	2	2	4	4	5	6	6	8	6	8	6	7	6
Caloric intake, per cent of addiction mean	96	89	62	51	57	68	68	55	59	83	79	76	74	80
Decrease in body weight (per cent)	0	0	0 3	2	2 1	1 7	1 5	2 0	2 4	3 6	3 5	3 5	2 5	2 2
Hours of sleep	10 7	7 1	5 2	6 0	5 5	6 0	5 4	4 8	3 6	4 6	6 2	6 2	6 4	
Average daily point score	4	10	13	19	22	23	27	22	33	27	26	23	25	23

*Figures represent average values for all 5 men

CHOICE OF DRUGS BY SUBJECTS AFTER
EXPERIENCE WITH METHADON

After observations were completed on the subjects who were addicted to methadon, they were offered their choice of a single dose of morphine, heroin, "dilaudid" (dihydromorphinone hydrochloride) or methadon. All the men elected to take one of the opiates, but after receiving the drug they were dissatisfied and complained that the sensations produced by the opiates no longer satisfied them. They asked for methadon, and when they received it they stated that methadon was the best drug and had the most desirable and long-lasting effects. These men were recalled at

TABLE 11—*Measurable Signs of Abstinence Following Withdrawal of Morphine After 28 Days of Addiction to 80 Milligrams Daily*

Sign	Day of Abstinence*					
	1	2	3	4	5	6
Rectal temperature, elevation above addiction mean	0.25C (0.49F)	0.5C (0.9F)	0.5C (0.9F)	0.4C (0.72F)	0.3C (0.54F)	0.25C (0.49F)
Morning systolic blood pressure, elevation above addiction mean (millimeters of mercury)	6	16	15	13	12	12
Respiratory rate, increase above addiction mean	2	5	6	4	5	5
Caloric intake, per cent of addiction mean	47	66	92	106	120	123
Decrease in body weight (per cent)	0.15	2.6	2.6	1.7	1.0	0
Hours of sleep	9.7	4.0	5.6	5.2	6.6	6.1
Average daily point score	19	34	26	22	17	14

*The figures represent average values for 19 subjects.

intervals for six months and again offered the choice of either an opiate or methadon. In the great majority of instances they chose methadon. The men who had been addicted to methadon spread the fame of the new drug among the patients who had never received it, and many addicts who never had experience with the drug are now asking for it in preference to morphine.

COMMENT

The results leave no doubt that methadon possesses all the characteristics of an addicting drug. In sufficient dose, it produces unmistakable euphoria, which is longer lasting than that produced by morphine. The euphoria may also be of a quality which is particularly pleasing to morphine addicts or to persons prone to addiction. The psychologic changes and the alterations in behavior during addiction to methadon are strikingly similar to those seen during addiction to morphine. Patients addicted to methadon, like those addicted to morphine, will increase the dosage

to the limit of their tolerance and after recovery which follows withdrawal will take additional doses of the drug at any opportunity All these facts point to the development of strong habituation (emotional dependence) in the cases studied Tolerance to many actions of the drug was clearly demonstrated Methadon will prevent the appearance of signs

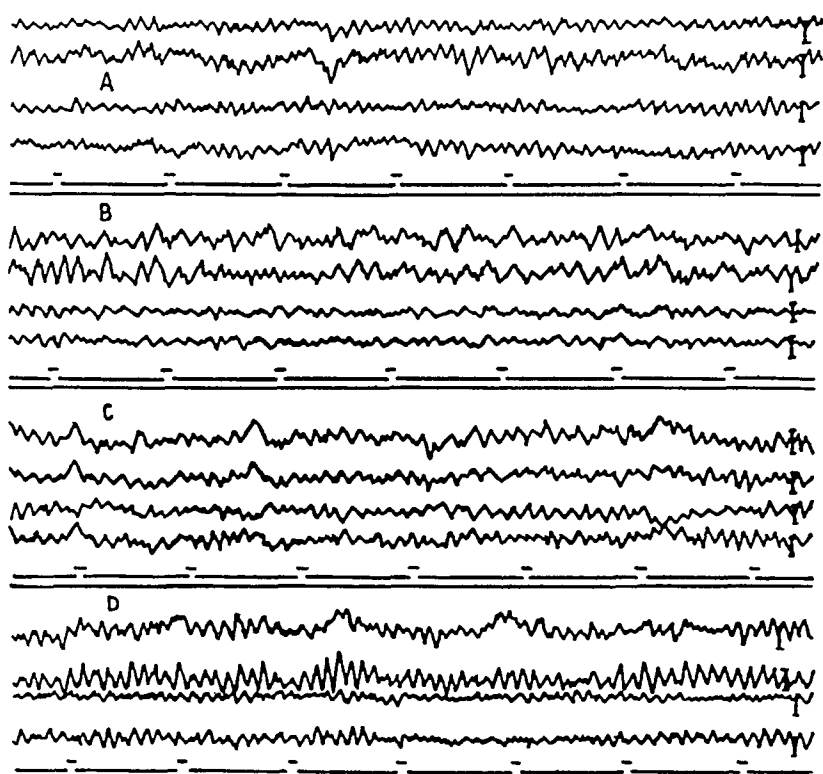


Fig 6—Tracings of electroencephalograms during twenty-nine days of continued administration of methadon in subject 728 In all records the uppermost tracing is left precentral monopolar, followed in order by right occipital bipolar, precentral bipolar and occipital bipolar The time is in seconds and the calibrations 25 microvolts *A*, control (preaddiction), the record is normal, with a mean alpha frequency of 9.3 cycles per second *B*, twentieth day, dose level is 30 mg four times daily and the total amount administered 0.9 Gm Note marked slowing of record Alpha activity is reduced, and the dominant rhythms are in the 4 to 6 cycles per second range, especially in the monopolar tracings *C*, fifth day of abstinence, considerable 4 to 6 cycles per second activity is still present *D*, fifteenth day of abstinence, the record is entirely normal and comparable to *A*, with a mean alpha frequency of 9.7 per second

of the morphine abstinence syndrome A definite though mild grade of physical dependence occurred after prolonged administration of large doses of methadon Methadon has been included under the provisions of the Harrison Narcotic Act in the United States, but unless arrangements can be made to limit the amount manufactured in all parts of the world, addiction to it may become a serious problem

Since the degree of symptoms of abstinence following withdrawal of methadon is mild, certain observers who feel that the production of a

strong grade of physical dependence is the only distinguishing characteristic of a drug which produces addiction may object to the classification of methadon as such a drug. This view is fraught with danger. Physical dependence is probably the least important characteristic of a drug which leads to addiction and is the only manifestation of addiction which is easy to treat. Morphine addicts are repeatedly cured of their physical dependence yet return again and again to the use of the drug, not because they are suffering from a withdrawal illness but because they enjoy the sensations produced by it and because they have substituted the use of morphine for the chief aims and objects in life (are emotionally dependent or habituated). The euphoria produced by methadon and the habituation seen during and after addiction to the compound are sufficient reasons for regarding it as a drug which produces addiction, even if no physical dependence followed its prolonged use.

Others might be inclined to minimize the danger of addiction to methadon because euphoria^{4b} is seldom seen after the administration of therapeutic doses to persons who have never been addicted to morphine. This fact has little importance, since addiction seldom begins as a result of the legitimate administration of therapeutic doses of a drug for medical reasons. In our experience, less than 5 per cent of 15,000 persons admitted to an institution for the treatment of morphine addiction were addicted because morphine was prescribed for them during an illness. The danger of "medical" addiction is great only when physicians believe that a substance does not lead to addiction and are careless in prescribing it. Addiction most often results when a susceptible person takes a drug in order to enjoy the euphoria which it produces or the temporary relief from emotional problems which it gives. Prospective addicts are nearly always introduced to the use of the drug by persons already addicted. For this reason, a drug which is popular with so-called secondary addicts (former morphine addicts who become addicted to a new drug) is extremely dangerous, since such persons are acquainted with the methods of acquiring and selling drugs illegally and have few scruples about introducing persons who are not addicts to the use of the drug. A drug which is popular only with "primary" addicts (persons never previously addicted to morphine who become addicted to a new drug) is much less dangerous, since it requires some time for "primary" addicts to obtain the education and contacts necessary for illegal trafficking in narcotics.

Our experiments may also be criticized on the ground that we used former morphine addicts as subjects and because such large doses were used. Aside from the fact that former addicts are the only subjects who can be used for such experiments, they are perhaps the best subjects, since information can be gained on the effects of a new drug on persons who are known to be prone to addiction. The question of dosage is also

easily answered. Addicts do not use small therapeutic doses. They increase the dosage of a drug to the limit of their tolerance, so that if the conditions of natural addiction are to be simulated, high doses must be used experimentally in evaluating the liability of addiction to new drugs.

The electroencephalographic changes appearing during continued administration of methadon are in general similar to those occurring during chronic intoxications with other sedative drugs, such as pyrahexyl compound²⁶. Of particular importance, however, is a comparison of the effects of methadon addiction with those reported by Andrews²⁷ during morphine addiction. While the changes are qualitatively almost identical, they are apparently much more severe during methadon addiction, since the records shown by Andrews^{27b} pertaining to "the most strongly addicted individual studied" in his group were similar to those of most of our subjects. Tolerance is probably developed more rapidly during morphine addiction. It is not possible from a study of Andrews' published observations on the electroencephalogram in cases of morphine addiction to compare the two drugs with respect to the changes during the period of abstinence. However, it is evident that abnormally slow activity, indicative of continued action of the drug, persists for at least two to five days after abrupt withdrawal of methadon.

The abstinence syndrome which develops after the withdrawal of methadon differs both qualitatively and quantitatively from the morphine abstinence syndrome. Qualitatively, the most striking differences following the withdrawal of methadon are the lack of muscle aches and cramps, the paucity of signs of autonomic dysfunction and the low incidence of vomiting and diarrhea. Quantitatively, the onset of abstinence is slower, the intensity of the abstinence is mild and the syndrome is prolonged. The slow onset and low intensity of symptoms of abstinence from methadon and the slow return of the electroencephalographic pattern to normal in man might possibly be related to a slow rate of metabolism of methadon as compared to that of morphine or to differences in the storage or excretion of the two drugs. Such a hypothesis cannot be proved or disproved until an adequate method is available for the determination of methadon in tissues and in biologic fluids.

In dogs, the syndrome of abstinence from methadon begins sooner, is more intense, and is shorter in duration than the syndrome of abstinence from morphine.⁷ This difference possibly might imply a more

26 Williams, E. G., Himmelsbach, C. K., Wikler, A., Ruble, D. C., and Lloyd, B. J. Studies on Marihuana and Pyrahexyl Compound, *Pub. Health Rep.* 61:1059-1083 (July 19) 1946.

27 Andrews, H. L. (a) Brain Potentials and Morphine Addiction, *Psychosom. Med.* 3:399-409 (Oct.) 1943, (b) Changes in the Electroencephalogram During a Cycle of Morphine Addiction, *ibid.* 5:143-147 (April) 1943.

rapid rate of metabolism of methadon as compared with metabolism of morphine in the dog or differences in the storage or excretion of the drugs

The mildness of the withdrawal symptoms after substitution of methadon for morphine indicates that methadon may be the agent of choice for withdrawal of opiate drugs from drug addicts. This problem is under investigation.

SUMMARY

1 Methadon relieved the symptoms of abstinence from morphine

2 Methadon prevented the appearance of signs of physical dependence when substituted for morphine at a level of 1 mg of methadon for each 4 mg of the stabilization dose of morphine. Once substitution was effected, the dose of methadon could be rapidly reduced without signs of abstinence appearing. After withdrawal of methadon, which had been substituted for morphine, a definite abstinence syndrome appeared which was slower in onset and milder in intensity than the syndrome of abstinence from morphine.

3 Fifteen volunteers who were former morphine addicts were given methadon to produce addiction for twenty-eight to one hundred and eighty-six days. The psychologic changes and the general behavior of the subjects resembled those seen during morphine addiction. No serious toxic effects were noted even though the dosage was increased to 400 mg daily in some cases. A mild normocytic nonprogressive anemia developed in 5 cases after three months of addiction. Fasting blood sugar content and intravenous dextrose tolerance tended to be low during addiction. Inflammation, induration and hypesthesia developed in the skin over the injection sites. Electroencephalographic patterns were slowed. All the men showed evidence of sedation when four doses of 10 mg or more were given daily. The sedative action appeared to be cumulative. Systolic blood pressure, respiratory rates and pulse rates were depressed throughout addiction. Rectal temperatures were decreased early in addiction and increased thereafter.

4 Tolerance to the following effects of the drug developed as addiction progressed: pain-threshold-elevating action, sedative action, effect on the electroencephalogram, miotic action, depression of caloric intake and probably circulatory and respiratory actions.

5 After abrupt withdrawal of methadon, a definite abstinence syndrome ensued which was characterized by complaints of weakness, fatigue, anxiety, vague abdominal discomfort, anorexia, insomnia, slight fever, elevation of systolic blood pressure, tachycardia, depression of caloric intake, slight loss of weight and alteration of glucose tolerance curves. Signs of abstinence did not appear until the third day, reached maximum in-

tensity on the sixth day and had not subsided completely at the end of the fourteenth day. The average intensity of symptoms of abstinence, as measured by the Himmelsbach scoring system, was mild. The syndrome of abstinence from methadon differed from the morphine abstinence syndrome in that few signs of autonomic dysfunction were observed, the onset of abstinence was slower, the intensity was milder and the course was prolonged. Electroencephalograms did not return to normal for two to five days after withdrawal.

6 The following evidence for the development of habituation (emotional dependence) to methadon was observed: euphoria after repeated small doses (or single large doses), behavioristic and psychologic changes resembling those in morphine addiction, requests for increases in dosage during addiction, requests for methadon following addiction and preference for methadon over all other drugs.

CONCLUSION

Methadon is an addiction-producing drug. The same precautions should be observed in prescribing methadon as are used in prescribing morphine.

PROGNOSIS IN LATE LATENT SYPHILIS

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LATE LATENT syphilis presents a therapeutic problem that is unique. A patient with syphilis in this stage suffers no discomfort or disability as a result of his infection, and he is not a menace to the public health, for syphilis is transmissible only in its early stages. If any benefit is to result from treatment, it must be, therefore, through a reduction in the frequency of subsequent clinical progression. It is common for patients with untreated syphilis to live normal lives, and it is impossible to demonstrate that the treatment of latent syphilis in a particular person has improved his outlook at all. Only by comparing final results in large numbers of patients, treated and untreated, can it be shown that the prognosis in latent syphilis can be altered by therapy. The evidence available on this point is incomplete, and a convincing proof of the effectiveness of antisyphilitic therapy is lacking.

Even though late latent syphilis does not produce symptoms, it is of great clinical importance since it is by far the most frequent form of the disease. It is also of importance because of the anxiety and social disruption to which it may lead as a result of the stigma that is universally attached to a diagnosis of syphilis.

For many years we have felt that latent syphilis is ordinarily over-treated, with the production of a great deal of needless anxiety and distress that is out of proportion to the amount of prevention of disability attained. Because of this belief and as a possible means of assessing the value of treatment, we have made it a policy in the Stanford Clinic to permit patients of more than 50 years of age to remain untreated provided that the infection was entirely latent and that the spinal fluid was normal. This group of intentionally untreated patients has grown to about 800, with a number of them under observation for over ten years, and a check-up on the outcome in this group was the beginning of the present investigation.

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The recent literature on the outcome of latent syphilis is scanty. The Cooperative Clinic group¹ studied a series of 1,936 cases of latent syphilis and reported the results in a number of papers in 1932 and 1933. Most of the conclusions relating to prognosis were based on 1,013 patients who were followed for two years or more. Discker and others² in 1944 studied a group of 5,326 patients but limited their analysis to 926 who had been under observation for a minimum period of five years. Jordon and Dolce³ in 1946 decided arbitrarily that reliable observations on the outcome in latent syphilis could not be obtained except in regard to patients who had been under observation for at least ten years, and they reported a study of 169 such patients.

In each of these investigations, patients were included who had both early and late latent syphilis. In early syphilis, which is generally considered to indicate the first four years of the infection, one is dealing with a stage of the disease in which mucocutaneous relapse is the usual type of recurrence, with late cardiovascular or nervous system involvement or gummas unlikely to appear for many years. In late syphilis, on the other hand, infectious lesions occur so infrequently that transmissibility can be dismissed from consideration, while the serious late lesions of syphilis are a constant threat. Unless these two stages of latent syphilis are considered separately, any attempt to estimate the prognosis must result in confusion.

The present study is limited to late latent syphilis, the diagnosis being based on the absence of symptoms or physical signs of the infection and a known or presumable duration of more than four years. In many cases the time of inoculation was not known, but no cases were included in which there was anything to suggest a duration of less than four years. Inasmuch as we observed no mucocutaneous relapses, it is unlikely that any significant number of patients had early infections.

The cerebrospinal fluid was examined in all instances in which the patients would permit this procedure. If the fluid contained evidence of the disease at the initial examination, whether before or after the institution of treatment, the patient was excluded from the series as having asymptomatic neurosyphilis instead of true latent disease. The spinal fluid was examined at least once in 55 per cent of the cases.

Fluoroscopic examinations of the chest were made on 41 per cent of the patients, and those showing definite evidence of aortitis before treat-

1 Moore, J. E., and others. Cooperative Clinical Studies in the Treatment of Syphilis. Latent Syphilis, *Ven. Dis. Inform.* 13: 317, 351, 371, 389 and 407, 1932, 14: 1, 1933.

2 Discker, T. H., Clark, E. G., and Moore, J. E. Long-Term Results in the Treatment of Latent Syphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* 28: 1, 1944.

3 Jordon, J. W., and Dolce, F. A. Latent Syphilis. A Study of One Hundred and Sixty-Nine Cases Observed Ten Years or More, *Arch. Dermat. & Syph.* 54: 1 (July) 1946.

ment or at the initial examination if it was relatively early in the course of therapy were excluded

No one was included who had a history of neurologic disease suggestive of neurosyphilis or who had had anything resembling benign tertiary lesions prior to entry to the clinic

The present series comprises a total of 2,566 patients with late latent syphilis, with 1,682 followed for one year, 628 followed for five years and 316 followed for nine years or more. The distribution of these patients according to race and sex is shown in table 1

Among the white patients we have included a group of slightly more than 300 non-Caucasians such as oriental, Filipinos and American Indians. These do not form a group that is large enough for separate analysis, but in no respect do they differ significantly from the Caucasians, and their inclusion does not alter the results of the analysis in any way that we have been able to discover

In the previous studies of latent syphilis, little or no correlation has been noted between the results of the serologic tests and the clinical outcome. We have been unable to show any relationship between the sero-

TABLE 1—*Distribution of Cases by Race and Sex*

	White	Negro	Total
Male	1,204	268	1,472
Female	696	398	1,094
Total	1,900	666	2,566

logic and the clinical response, and nothing is to be gained by presenting the data. The tests have been performed in several laboratories and by technics that have varied greatly with the passage of time, and any conclusions that might be drawn from them would be distinctly unreliable

The present study is entirely a clinical one, and a patient who remains in the latent stage is classified as unchanged, regardless of his serologic status. The progression is used to indicate that there has appeared definite or probable clinical evidence of syphilis during the period that the patient has been under observation in the clinic. Progression is of several types, which are described here

Central nervous system progression is that in which an initially negative reaction of the spinal fluid becomes positive or in which definite clinical evidence of neurosyphilis develops or both. No case is included in which the spinal fluid had not been normal initially

Cardiovascular progression is the term used for patients in whom aortic regurgitation or aneurysm or definite evidence of aortitis develops during observation as determined by roentgenologic study or in whom aortitis is found at autopsy

Gummatous progression indicates lesions of the skin, bone or soft tissue, clinically syphilitic, that respond promptly to antisyphilitic therapy. No visceral gummas were observed in this study.

Probable progression refers to several types of cases. In some, definite clinical evidence of syphilis is detected later, but in retrospect it appears that the initial findings did not justify a diagnosis of latency. However, since such a diagnosis was made on the patients' entry to the clinic, these cases are not excluded. In some, there may be noted a slight increase in the diameter of the aorta, not sufficient to warrant their inclusion as examples of true cardiovascular advance. In a few cases symptoms related to the nervous system develop, such as hemiplegia suggestive of neurosyphilis in the absence of any other cause, in spite of a normal spinal fluid. Acute or subacute iritis or uveitis in a patient with latent syphilis has been classed as a probable progression, since proof that such lesions are due to a coincident syphilis is nearly always impossible to establish. We have considered these cases carefully and feel that they should be counted as treatment failures, but it is less confusing to maintain them in this separate category.

TABLE 2 — *Progression in Relation to the Minimum Period of Observation According to Race*

Minimum Observation Period in Years	White Per Cent Progression	Negro
9	33	47
5	36	52
3	39	44
1	35	18
0 (entire series)	24	11

A few patients have died, but in all instances the cause of death was known from death certificates or from autopsy reports and each patient could be classified as unchanged or assigned to the proper category of progression without considering them in a separate group.

It has been customary in the past to limit studies of this type to patients who have been under observation for certain minimum periods. The periods selected by various investigators have probably been determined by the quality of their follow-up observations. As was noted previously, the Cooperative Clinical group¹ selected two years, Discker and others² five years and Jordon and others³ ten years as their minimum observation periods. In general it has been assumed that the longer the required time of observation, the more accurate will the appraisal be. It has also been customary to express the rate of progression as a percentage of the number of patients who satisfy the requirements for admission to the series. On this basis, progressions should be excluded, no matter how definite they may be, when they occur in patients who have not been under observation for the selected period.

The analysis of our data was started in the conventional way, with the thought that the material might adapt itself particularly well to some special period of observation. We were greatly confused when we discovered that the results could be varied markedly by changing the minimum period of observation. A typical example of this difficulty is shown in table 2, in which the incidence of progression in Negroes and in white persons is compared, all other variables except the minimum period of observation being disregarded.

It is evident from table 2 that when the longer periods of five and nine years are required the prognosis appears poorer for the Negro than for the white person. With a three year period, the results in the two races are almost the same, and when the period is less than three years, Negroes have distinctly the better of it. Similar results are also obtained when factors other than race are analyzed in this way. Such results cannot be correct, and there must be, therefore, some concealed fallacy that leads to this confusing situation. The principal fallacy responsible for this difficulty probably lies in variations in the adequacy with which different groups can be followed. In general, patients who are uncooperative will disappear, and only a few will remain under observation for the longer periods. In these circumstances, the late return of a small number of patients by reason of illness from progressive syphilitic disease will have a profound effect on the per capita incidence of relapse. On the other hand, among cooperative patients who return for routine periodic examinations over periods of years the occasional reappearance of a patient because of illness will not alter the incidence of failure materially. Moreover, in cooperative groups progressions usually will be detected earlier and will be enumerated at a time when larger numbers of well patients remain under observation, and the per capita incidence of relapse will be modified to a lesser degree.

Although the mechanism by which variations in follow-up affect the incidence of progression is conjectural, as just presented, we feel sure of the fact that they do affect it. In our material there is a high degree of correlation between progression and cooperation whether the data are analyzed according to race, sex, age, previous treatment or treatment in our own clinic. The consistency of this finding has convinced us that there is a fundamental fallacy in the expression of relapses on the per capital basis and also in the requirement of an arbitrary minimum period of observation. We have, accordingly, set out to evolve a method of analysis that is less subject to these errors.

Because of the long duration of latent syphilis, the necessity for a reasonable minimum period of observation to ensure reliable conclusions at first seems self evident. On reconsideration, however, in view of the confusion encountered when such a period is required, it becomes obvious

that this stipulation is absurd. The minimum observation period starts when the patient is first examined and the diagnosis made. Since the disease is symptomless, this moment is purely the result of chance and is completely without significance in relation to the course of the disease. In some cases the infection will have occurred as recently as four years before the first visit and in others the patient may first appear on the eve of death. In the former instance a ten year period would be inadequate since late progressions are unusual in less than fifteen or twenty years. In the latter situation a few days would provide a complete solution if the cause of death could be proved to be either due to syphilis or unrelated to it. With a large series of cases observed at random throughout the entire course of latency, one should be able to obtain an accurate picture of the prognosis in latent syphilis in a relatively short period. The important factor in a proper appraisal is not the number of patients observed for a specified time but rather the total duration of observation of all patients together, or the patient years of observation.

If we should study 1,000 patients with latent syphilis who have been observed for a period of one year, we would have one thousand patient years of latent syphilis for analysis. This thousand years would cover the entire course of latency and should be an entirely representative sample. If we require an arbitrary ten year observation period, only 100 patients will be necessary for one thousand years of observation, but these 100 patients will by no means be a random sample of the entire population with latent syphilis. Only a small fraction of patients can be followed for ten years, and although one cannot define the exact way in which they differ from their less cooperative fellows, there is no question that they constitute an especially selected group and that conclusions as to the outcome of latent syphilis based on such a group will probably be subject to serious bias. Any minimum observation period leads to an automatic selection and the introduction of errors that cannot be tolerated in statistical analysis. If progressions are computed in relation to the total years of patient observation instead of on a per capita basis, these errors are largely avoided, as will be demonstrated.

The conception of patient years as a basis for investigation is not new and has been used for many years in life insurance studies. This type of analysis is applicable only in situations in which the patient is first seen purely by chance at a time that is unimportant in relation to his disease. It could not be used for any other stage of syphilis in which symptoms of the infection would be a factor in causing patients to seek medical care.

The present analysis of the prognosis in latent syphilis and of the effect of treatment on it is based entirely on the frequency of clinical progression per patient year of observation. In order to avoid small

figures, the incidence of relapse will be multiplied by 100 and will be given in terms of patient centuries of observation, designated as "per century" for the sake of brevity. This method of study permits the inclusion of a large number of patients observed for short periods who would otherwise have to be eliminated, which results in a great augmentation of the total data and provides a more representative sample of late latency. Moreover, it does not require the exclusion of progressions because they happen to have been noted within an arbitrary minimum period. Observation periods in this study have been computed to the nearest year, and the shortest time considered is therefore just over six months.

As an example of the divergent results that are obtained by these methods of analysis, a comparison of two groups of patients is presented in table 3. Those classed as untreated comprise the group mentioned previously who were purposefully followed as controls. Those classed as uncooperative were placed on treatment and every attempt was made

TABLE 3—*Incidence of Progression in 2 Groups of Patients Estimated by the Per Capita Method in Comparison With the Total Period of Observation Scheme Incidence of Progression*

Patient Group	Incidence of Progression Per Capita, %	Per Century of Patient Observation
Untreated	5.3	1.06
Uncooperative	10.9	0.85

to give them conventional therapy, but by their own choice none of them received more than a total of twenty-four injections and most of them were almost untreated. In the per capita computation a minimum observation of five years is used, as was done by Disker² and others.

The per capita figures show a failure rate twice as great among the patients who received small amounts of treatment as among those who had none at all. This is in accord with a frequently expressed theory that a little treatment is worse than none, a notion that has never seemed reasonable when applied to a disease with a long-established immunity such as late latent syphilis. When progression is computed in relation to the total observation period, the results are reversed, which suggests that even a little treatment may be of benefit. Here again the per capita method shows an erroneously high incidence of progression in patients who are poorly followed, a fault which we believe is diminished considerably by the use of the per century system.

As a further test of the validity of the computation of progressions in terms of total observation, table 4 has been prepared. It is assumed in the use of this method that any one year of patient observation is as good as another. If this be true, progressions should occur with equal frequency in the first, second, fifth or any other particular year after the

beginning of our period of observation In table 4 the frequencies of the various types of progression per patient century of observation are compared according to whether the progression occurred during the first five years of observation or after

It is readily seen that the incidence of progression of the various types is practically identical, a strong indication that this method of computation is valid

Although we are interested primarily in the effect of treatment on the prognosis in latent syphilis, there are several other factors that have some bearing on the outcome and should be considered first The most important of these are race, sex and age Progressions in relation to race and sex without regard to treatment are presented in table 5

TABLE 4—*Incidence of Progressions Per Century of Observation According to Duration of Observation*

Type of Progression		Progressions per Century of Observation		
		First 5 Years of Observation	Over 5 Years of Observation	Total Observation
Nervous system	-- --	0 06	0 03	0 05
Cardiovascular	-- --	0 13	0 19	0 16
Gummatous	-- --	0 15	0 19	0 17
Probable	-- --	0 25	0 26	0 25
Total	-- --	0 60	0 68	0 63
Centuries of observation	-- --	52 1	30 9	83 0

TABLE 5—*Frequency of Progressions in Relation to Race and Sex*

Type of Progression		Progressions per Century of Observation			
		White	Negro	Male	Female
Nervous system	-- --	0 06	0 00	0 04	0 06
Cardiovascular	-- --	0 16	0 15	0 24	0 03
Gummatous	-- --	0 17	0 15	0 18	0 15
Probable	-- --	0 26	0 22	0 32	0 15
Total	-- --	0 65	0 51	0 79	0 39
Centuries of observation	-- --	69 4	13 7	49 5	33 5

There is little difference in incidence of progressions of the various types in white and in Negro patients In contrast to the usual opinion, it appears that Negroes may have a little the better of it The difference between these results and those obtained by the per capita method of analysis, with long minimum periods of observation as in table 2, is probably explained on the basis of the degree of follow-up cooperation that can be obtained from white and Negro patients Negroes are notoriously difficult to follow and will consequently show a high failure rate by the per capita computation because of a fallacy in that method of analysis that should be eliminated when the total observation period is used as a basis for reference We do not propose that our material is of sufficient magnitude to disprove the established notion that syphilis is more serious in Negroes than in white persons, but we do feel that the racial prognosis is not as different as has been supposed

When progression is considered in relation to sex, it is evident that it is more frequent in males. This finding is in accord with the usual opinion and agrees with computations made by the per capita method. However, there is no significant difference in the degree of cooperation, and the principal fallacy of the per capita method is therefore lacking.

The effect of the age of the patient is indicated in table 6. Here the frequency of the various types of progressions is compared in two groups of patients. The first group were less than 35 years of age at the time of entry to the clinic and the second were over 35. For all types of progression except that in neurosyphilis the older patients have a distinctly higher rate. These figures do not indicate whether or not there is an upper age limit above which the incidence of progression declines, and our data are inadequate to determine this.

Our principal concern is with the effect of treatment on the prognosis in latent syphilis. For the investigation of this question, it is necessary to divide treatment into two main types, i.e., that given before admission to the clinic and that administered in the clinic under direct

TABLE 6—*Frequency of Progressions in Relation to Age*

Type of Progression	Progressions per Century of Observation,	
	Under 35 at Entry	Over 35 at Entry
Nervous System	0 05	0 04
Cardiovascular	0 08	0 22
Gummatous	0 08	0 24
Probable	0 19	0 30
Total	0 41	0 80
Centuries of observation	36 9	46 1

supervision. The data on previous treatment are, of course, inaccurate, being based almost entirely on the history obtained from the patient, with occasional substantiation in reports from physicians. It is usually possible, however, to obtain a general idea of the treatment received, and, as will be shown, great accuracy is probably not too important.

The amount of treatment received by our patients prior to entry varied widely, and our material is unlike that of Discker and others, who found in their series so little previous therapy that they were able to disregard it. We have classified previous treatment into three types. "Insignificant" indicates no therapy, a few scattered injections or treatment with mercury alone. The majority of patients in this group had had no treatment at all. "Adequate" indicates that the patient had received forty injections of arsenic or bismuth within a period of one year or somewhat more if it was irregular.

"Inadequate" indicates treatment that falls between the two previous types. One thousand two hundred and eighty-eight patients had had insignificant treatment, 762 inadequate treatment and 516 adequate treatment.

When the data were analyzed, it was found that there was no discernible difference in the composition of the groups receiving adequate and inadequate treatment or in the prognosis, and in the subsequent analyses these two groups were combined into a single group designated as having had significant treatment in contrast to the remaining group who had insignificant treatment. The observations presented in table 7 show the close agreement between these groups that justifies this combination.

The frequency of progression according to the treatment received before entry to the clinic is shown in table 8. All forms of progression are distinctly less frequent when the patients have had some treatment prior to admission to the clinic. In fact, the difference in prognosis in the two groups is probably greater than the figures in table 8 indicate because of differences in their composition. The most important dif-

TABLE 7—*Composition of and Prognosis for Groups Receiving Inadequate and Adequate Treatment Prior to Entry*

	Adequate	Inadequate	Significant
Total patients	516	762	1 278
Observed over 1 year.....	56%	59%	57%
Average observation.....	2 0 yr	2 6 yr	2 3 yr
Average age at entry.....	36 9	36 8	36 9
Average duration of infection	14 0 yr	14 8 yr	14 5 yr
White males	41%	46%	44%
White females	31%	25%	28%
Negro males.....	14%	12%	12%
Negro females	14%	17%	16%
Progressions per century of observation.....	0 39	0 45	0 43

TABLE 8—*Frequency of Progressions in Relation to Previous Treatment*
Progressions per Century of Observation,
Previous Treatment

Type of Progression	Insignificant	Significant
Nervous system	0 08	0
Cardiovascular	0 19	0 10
Gummatous	0 19	0 13
Probable	0 28	0 20
Total	0 74	0 43
Centuries of observation	52 3	30 0

ferences is that patients who had had insignificant treatment received more treatment after admission than did those who had significant previous therapy, which should result in a definite improvement in prognosis.

Treatment received after admission to Stanford Clinic is divided into four classes. The term none is used in relation to the group of patients mentioned previously who were selected at the initial examination for observation without treatment. Some of these had had previous treatment, but many were included who had had no previous treatment. Poor treatment consists of less than twenty-five injections of any kind during the patient's entire observation period. Fair treatment indicates a total

number of injections between twenty-five and sixty-five, and good therapy refers to more than sixty-five doses. Injections of arsenic and heavy metal have been combined in order to simplify the analysis. In most cases, arsenical injections made up from one fourth to one third of the total. The comparative results of treatment administered after admission to the Stanford Clinic are shown in table 9.

Here it is seen that increasing amounts of treatment consistently lead to improved therapeutic results. A few minor inconsistencies, such as the occurrence of the only nervous system advances in a single group, are probably not significant. The various groups are comparable in make-up in regard to age and sex distribution except for the untreated patients.

TABLE 9—*Frequency of Progressions in Relation to Treatment Received at Stanford Clinic*

Type of Progression	Progressions per Century of Observation			
	Type of Treatment Received,			
	None	Poor	Fair	Good
Nervous system.	0	0	0 25	0
Cardiovascular	0 37	0 21	0 12	0 03
Gummatous	0 37	0 43	0	0 03
Probable	0 32	0 21	0 43	0 15
Total	1 06	0 85	0 80	0 21
Centuries of observation.	18 9	14 1	16 2	33 9

TABLE 10—*Total Incidence of Progression Per Century of Observation in Relation to Treatment at Stanford Clinic According to the Amount of Previous Treatment*

Treatment at Stanford Clinic	Previous Treatment	
	Insignificant	Significant
None or poor	1 32	0 58
Fair	1 04	0 46
Good	0 23	0 13

These averaged 11 years older than the other patients, and a higher proportion of them were males. Both of these factors have an adverse effect on the prognosis aside from the lack of treatment. It is probable that there is little difference in the untreated and poorly treated groups as a result of treatment, the latter having had almost no therapy because of lack of cooperation. However, the progressive improvement with fair and good treatment leaves no doubt as to the value of antisymphilitic therapy in late latent syphilis.

In table 10 the incidence of advance is shown in relation to treatment before admission to the clinic as well as after admission. Previous treatment has been administered relatively early in the course of the infection, some of it at the onset, in contrast to the therapy after admission, all of which is given late in the disease. It is evident from table 10 that both types of treatment have a definite effect on prognosis and

that treatment at any time is a factor in reducing the incidence of progressions in late latent syphilis

Significant previous treatment reduces the frequency of advance to just about half in each treatment category, and good treatment before and after entry to the clinic results in a tenfold improvement in prognosis

COMMENT

Evaluation of prognosis in late latent syphilis according to the frequency of progression per century of patient observation is justified for several reasons. The conventional method of expressing progressions in percent of the total number of patients still under observation at the time of discovery of the relapse is subject to a serious but incalculable error. This error is the result of different degrees of cooperation from different groups of patients. Cooperative groups will have relatively large numbers of patients after long observation periods, and because of regular attendance, progressions will be detected early. Both of these factors make for a low incidence of relapse when computed on a percentage basis. Uncooperative groups, on the other hand, will have few patients still under observation after long periods. Progression is not likely to be detected on routine examination but will be evident when a patient is forced to return for medical advice because his disease has incapacitated him. This results in late discovery of serious advances at a time when few patients remain under observation and when such advances will have a considerable effect on the percentage of failures.

Under the century of observation system, the factor of cooperation is minimized. When a patient returns because of a progression, he is considered in relation to the total years of observation in his particular group and not merely as one of a small number of patients who have been observed for the period that has elapsed between his first visit and his reappearance late in the disease.

Another fallacy in the usual method of analysis is introduced by the requirement of an arbitrary minimum period of observation since patients who have not completed the selected follow-up period must be excluded even though they have shown definite progression. A minimum period of observation is essential in primary or secondary syphilis or in any other stage in which the diagnosis of syphilis is based on a definite episode in the course of the disease. In late latent syphilis, however, the beginning of the observation period is determined entirely by chance and has no fixed relationship to the progress of the infection. In these circumstances the first year of observation should be just as informative as the second or fifth or any other particular year. With a large enough series of patients, it should be possible to obtain an accurate appraisal of the outcome in a single year.

A true random sample of patients with latent syphilis can be obtained only by including every patient who is discovered to have syphilis in this stage. Many patients will not return after the first visit, and more and more will disappear after increasing periods. The patients who continue to return do not represent a random sample, and whether or not the causes of failure to return or of continued attendance have any relation to the outcome of the disease we do not know. It is obvious that we cannot base any conclusions on one visit patients about whose progress we know nothing, but it is evident that as the observation period becomes longer the sampling becomes less representative and conclusions more uncertain.

In this study we have included all patients who have been followed for six months or more. It is our custom to reexamine patients routinely at six month intervals, and in our material, for practical purposes, patients observed for less than six months are of the one visit type. Although we have thus set a minimum observation period, the patients excluded are really only those about whose course we have no information whatever. There may well be some bias in our sampling, but it is much less than would be introduced by a longer minimum period of observation.

The century of observation method gives a clearer conception of prognosis and of the influence of treatment than does the per capita method because it introduces the factor of time and thus furnishes some notion as to when a progression might be expected rather than a crude estimate of the total probability of progression, provided the patient lives long enough to have one. For example, in our two practically untreated groups (none and poor) there was approximately one advance per century of observation. For a patient of forty-five years who has a life expectancy of about twenty-five years, the chances that trouble will eventually develop would be 1 in 4. With adequate treatment, the incidence of progression is reduced to once in five centuries and the chance of eventual progression in the patient of 45 is only about 1 in 20.

The probability of advance cannot be determined directly from quantity of treatment and life expectancy as there is an increase in the incidence of progression with advancing age. In our material the percentage of progression in patients over 35 on entry was almost twice that in those under 35. The average ages of these groups have not been computed, but the older group probably averages in the fifties, with a life expectancy of about twenty years, and the younger in the late twenties, with an expected forty years to live. It would seem that the probability of eventual progression would be about the same in the two groups, namely, about 1 in 5, or 20 per cent. It is possible that there may be a reduction in the incidence of syphilitic lesions in the older

age group as the duration of infections continues beyond the time at which the peak incidence of late lesions occurs, but we have not been able to show this from our data

It is interesting that the expected incidence of eventual relapse in our little-treated group of about 20 per cent is approximately the same as that observed by Bruusgaard⁴ in his untreated patients with early syphilis after fifteen to forty years of observation provided patients with neurosyphilis are eliminated from his series, as was done for the most part in ours by the exclusion of all patients whose spinal fluids were initially positive

The value of antisyphilitic therapy in latent syphilis in preventing the late manifestations of the disease is clear. Even a small amount of treatment prior to entry to the clinic or relatively early in the disease has a profound effect in reducing the frequency of late lesions, and reasonably adequate therapy, both early and late, decreases the unsatisfactory results almost to insignificance. From our data it would seem that any amount of treatment given at any time prior to the development of late syphilitic lesions is effective in reducing the incidence of such lesions. Moreover, it appears that the improvement in prognosis varies in general with the amount of treatment, and we have no evidence of any leveling off in the improvement as the amount of therapy is increased above a certain figure. Our classification of fair treatment (twenty-five to sixty-five injections) corresponds roughly to the twenty arsenic and twenty bismuth injections considered adequate by Discker and others, and yet it yields, in our experience, results that are distinctly inferior to those obtained with larger amounts of therapy. We do not agree that the 20-20 treatment is sufficient but believe that the incidence of failure of treatment probably continues to decrease as the total treatment is increased.

There is no doubt in our opinion that the total observation method is both reasonable and valid in the estimation of the rate of progression in latent syphilis. For untreated patients there seems to be no question of its validity, but as regards treated patients, it is possible that we might be introducing an error by temporarily deferring a progression while therapy is being administered only to have it become evident a year or so later. If this were the case, the earlier part of the observation period in treated patients would be worthless. There are several reasons why this does not seem to be correct. In the first place, we have seen progressions of various types occur while patients were under treatment, and it is not to be expected that therapy would stop a progression that was imminent unless it was of the benign tertiary type and relatively unim-

⁴ Bruusgaard, E. Ueber das Schicksal der nicht spezifisch behandelten Luetiker, *Arch f Dermat u Syph* 157 309, 1929

portant More important, however, is the finding that progressions occur at the same rate during the first five years of observation as they do subsequently We believe, therefore, that the better results with increasing amounts of therapy reflect prevention of late lesions and not simply a deferment thereof

In the decision as to whether or not a person should be treated for late latent syphilis, the principal consideration is the probability of the development of cardiovascular involvement Although in one of our treatment groups we observed an incidence of disease of the nervous system of one per centum, it is probable that this type of failure could be eliminated by more thorough examination and by repeated tests of the spinal fluid Gummas and probable late advances are of minor importance as they usually respond well enough to therapy after they appear so that careful observation is as satisfactory a safeguard as antisypilitic therapy and is much less risky Cardiovascular disease, however, carries a grave prognosis after its development, and response to therapy is dubious at best, so that it can be controlled satisfactorily only by prevention

Cardiovascular progression in our material occurred about once in four centuries in the virtually untreated groups, the incidence being reduced to once in thirty centuries by good therapy This is an impressive effect of treatment and would seem to justify the thorough treatment of every patient with latent syphilis were it not for the fact that the total risk even in untreated patients is not great One has to take into account the patient's probable expectation of life and balance it against the hazards of therapy, not forgetting the emotional disturbances that often result, before deciding on whether or not to treat an individual patient In general it would seem not unreasonable to treat all patients with late latent syphilis who are in good health if they have not passed the age of 60 It should be pointed out that this opinion is in disagreement with that previously expressed by one of us (C W B),⁵ who formerly felt that the treatment of latent syphilis was probably not of sufficient benefit to the average patient to justify the risks it involves

The whole concept of treatment in latent syphilis may be changed by antibiotic therapy The use of penicillin in latent syphilis has been discouraged, at first because of a shortage of the material and later because it was felt that the results of its use could be determined only by means of an elaborately set up, prolonged experiment involving a tremendous number of patients The following statements from Moore's⁶ recent textbook on "Penicillin in Syphilis" summarizes current opinion

5 Barnett, C W Why Treat Latent Syphilis? *Stanford M Bull* 2 51, 1944

6 Moore, J E *Penicillin in Syphilis*, Springfield, Ill, Charles C Thomas, Publisher, 1947

The aim of treatment of latent syphilis is entirely preventive. There are only two measuring rods of its success or failure. The first and only important criterion of success is the extent to which the development of clinical manifestations of syphilitic disease has been prevented. To determine this point requires post treatment observation for many years, if possible until death and necropsy of large numbers of treated patients. A final evaluation of treatment results cannot be accomplished without such a study, which requires a minimum of 10-25 years for completion.

We believe that this attitude should now be changed since it seems possible to get an accurate estimate of the value of penicillin in latent syphilis in a comparatively few years provided a large number of patients selected at random are treated and that the incidence of progressions is determined on the basis of total observation period and not on a percentage basis. Since the use of penicillin is almost without risk and since the period of administration is short enough to eliminate most of the difficulties of interrupted or partial courses of treatment, there is no reason why a tremendous amount of data could not be collected in a number of clinics and a reasonable answer given to the question of the effectiveness of penicillin within a few years. Should penicillin prove effective, all arguments against the routine treatment of latent syphilis would vanish.

The total number of progressions observed in this study was small, there being but fifty-two in all. When these are broken down into various types and then are related to different amounts of treatment, their numbers become so small that proof of statistical significance is impossible. The results are, however, extremely consistent when analyses are made in respect to type of progression, age, race and sex of patients and amount of treatment. Such consistency is a valuable index of statistical reliability, and in this study we believe that it is adequate evidence of soundness.

SUMMARY

1 The prognosis for 2,566 patients with late latent syphilis was studied and is analyzed in relation to treatment.

2 The conventional methods of estimating progressions on a percentage basis and of requiring an arbitrary minimum period of observation before a patient is qualified for inclusion in the study are shown to lead to erroneous conclusions.

3 It is proposed that progressions be expressed in relation to total years or centuries of patient observation, without a minimum period of observation, and the present analysis is presented in this manner.

4 The prognosis in later latent syphilis appears to be improved by treatment at any time, and there seems to be steady improvement with increasing amounts of therapy. The conventional course treatment of

twenty injections of arsenic and twenty injections of bismuth is only about half of a truly adequate regimen

5 It is suggested that by the use of the proposed method of analysis it should be possible to determine the value of penicillin in latent syphilis in a few years, if a large group of patients were treated, rather than in the ten to twenty-five years previously thought necessary for such a study

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LYMPHOGRANULOMA VENEREUM IN A PATIENT WITH MEDIASTINAL LYMPHADENOPATHY AND PERICARDITIS

Isolation of the Virus from the Supraclavicular Lymph Node

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A PATIENT with unusual manifestations of systemic lymphogranuloma venereum was recently observed in this clinic. The patient had evidence of pericarditis and had supraclavicular and mediastinal lymphadenopathy. The infection was proved by the isolation of the virus.

Rare instances of systemic infection with lymphogranuloma venereum have been reported, but only a few of them have been proved by recovery of the virus.¹ This agent has been isolated from the spinal fluid of 1 patient with meningoencephalitis and from the conjunctival exudate in cases of blennorrhoea caused by lymphogranuloma venereum.² It has also been recovered from the blood and spinal fluid of a patient with genital lesions who had no other manifestations of the disease,³ which indicates that the virus may be widely disseminated in the course of this infection. Cutaneous lesions, arthritis and involvement of cervical, supra-

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1 (a) Sabin, A. B., and Aring, C. D. Meningoencephalitis in Man Caused by the Virus of Lymphogranuloma Venereum, *J. A. M. A.* **120** 1376-1381 (Dec 26) 1942. (b) Zarafonitis, C. J. D. Meningoencephalitis in Lymphogranuloma Venereum. A Report of Two Cases, *New England J. Med.* **230** 567-573 (May 11) 1944.

2 Scheie, H. G., Crandall, A. S., and Henle, W. Keratitis Associated with Lymphogranuloma Venereum, *J. A. M. A.* **135** 333-339 (Oct 11) 1947. Sabin and Aring.^{1a}

3 Beeson, P. B., Wall, M. J., and Heyman, A. Isolation of Virus of Lymphogranuloma Venereum from Blood and Spinal Fluid of a Human Being, *Proc. Soc. Exper. Biol. & Med.* **62** 306-307 (June) 1946.

clavicular, axillary or retroperitoneal lymph nodes have also been described as systemic manifestations of the disease⁴ The diagnosis in the cases involved was made from positive reactions to cutaneous tests, complement fixation test or histologic studies

REPORT OF A CASE

D B, an 18 year old Negro, experienced malaise, anorexia and cough six weeks prior to his admission to the hospital These symptoms were followed by mild precordial pain and loss of weight of 15 pounds (6.8 Kg) Because of his complaints, the patient came to the clinic, where a pericardial friction rub was heard He was admitted to the hospital for further study

The patient gave a history of three episodes of acute urethritis, the last occurring three months prior to his admission He denied having had tuberculosis, syphilis or rheumatic fever

He did not appear to be ill His temperature was 98.8 F, the pulse rate was 100 and the blood pressure was 140 systolic and 90 diastolic There were no lesions on the skin, mucous membranes or genitalia The only significant physical findings were a pericardial friction rub and a single, enlarged (2 by 2 cm) supraclavicular lymph node This node was discrete, mobile and nontender and was situated in the neck just above the right clavicle The other superficial lymph nodes were not remarkable The heart was not enlarged to percussion The rate was regular, and a grade II systolic murmur was present at the apex A low pitched, to and fro pericardial friction rub was heard over the precordium, loudest in the left fourth and fifth interspaces The remainder of the physical examination revealed nothing remarkable

Laboratory examination revealed a hemoglobin content of 15.5 Gm and a red blood cell count of 4,560,000 The white blood cell count was 9,100, with a normal differential count The sedimentation rate (Westergren) was 121 mm per hour The urine was normal The reaction to the Kahn test of the blood was negative Reactions to first and second strength tuberculin tests were also negative The Frei test ("lygranum") gave a strongly positive reaction The plasma protein content was 8.6 Gm per hundred cubic centimeters on admission, with 4.6 Gm of globulin and 4.0 of albumin Cephalin flocculation and formol-gel tests elicited positive reactions The thymol turbidity reaction was 21 units Examination of the spinal fluid showed it to be normal The complement fixation test for lymphogranuloma venereum gave a positive reaction with each of eight specimens of serum taken during the next three months "Lygranum" antigen (E. R. Squibb & Sons) was used All the samples of serum were tested at the same time and showed a complement-fixing titer of 1:640

4 Hickam, J. B. Cutaneous and Articular Manifestations in Lymphogranuloma Venereum Activation of the Disease by the Frei Test, *Arch Dermat & Syph* 51:330-336 (May) 1945 Costello, M. J., and Cohen, J. A. Lymphogranuloma Venereum Affecting Simultaneously Cervical and Inguinal Lymphatic Glands Report of a Case, *ibid* 41:557-561 (March) 1940 Koteen, H. Lymphogranuloma Venereum, *Medicine* 24:1-69 (Feb) 1945 Reichle, H. S., and Connor, W. H. Lymphogranuloma Inguinale Report of a Case with Involvement of Retroperitoneal Lymph Nodes and Probable Involvement of the Hip Joint, Adrenals and Kidneys, with Autopsy, *Arch Dermat & Syph* 32:196-203 (Aug) 1935

Roentgenographic examination of the chest revealed enlargement of the hilar lymph nodes and a slight increase in the cardiac silhouette (fig 1) Electrocardiographic studies showed changes in the S-T interval and the T waves compatible with pericarditis

During his stay in the hospital, the patient's temperature remained normal, but a pulse rate of 90 to 100 persisted On the fifth day the enlarged right supraclavicular lymph node was removed for histologic study, and a diagnosis of lymphogranuloma venereum was made The pericardial friction rub and the systolic murmur disappeared within a week Seven weeks after his admission a single, enlarged (3 by 3 cm) lymph node was found deep in the left supraclavi-

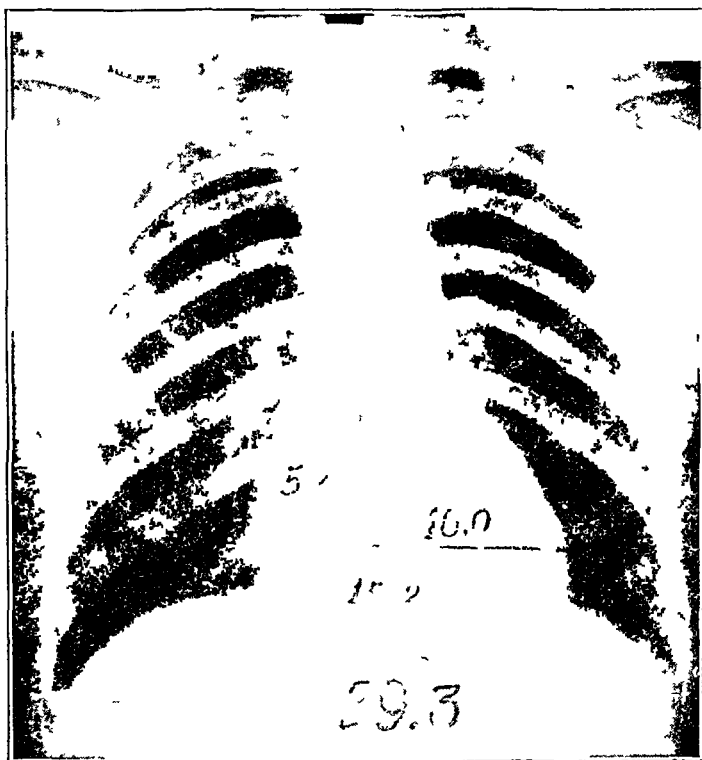


Fig 1—Roentgenogram of the chest showing enlargement of the hilar lymph nodes The transverse diameter of the heart is also increased

cular fossa This node was nontender and discrete It was excised for bacteriologic, virus and histologic studies During the next three months, the plasma protein content fell to 7.4 Gm per hundred cubic centimeters and the reaction to the formol-gel test became negative The abnormalities in the roentgenogram of the chest gradually disappeared The patient gained 30 pounds (13.6 Kg) of weight and was completely asymptomatic He had been treated with 4 Gm of sulfathiazole a day for one week, without change in his clinical course He has been observed for eight months since the onset of his illness and is now completely well

MORPHOLOGIC STUDIES

Two specimens of tissue were examined The first specimen was the right supraclavicular lymph node measuring 2.4 by 1.8 by 1 cm It was

submitted fixed in Zenker's fluid. The second specimen was a part of the left supraclavicular lymph node. It was partly covered by a grayish opaque capsule. The cut surfaces were grayish pink, with several pinpoint, yellow foci.

Histologic examination revealed a similar picture in the two specimens. Numerous small and large stellate abscesses were scattered through the node. The fully developed, older lesions had a necrotic center with polymorphonuclear leukocytes and cellular debris surrounded by a zone of large mononuclear cells (fig 2). These cells displayed a

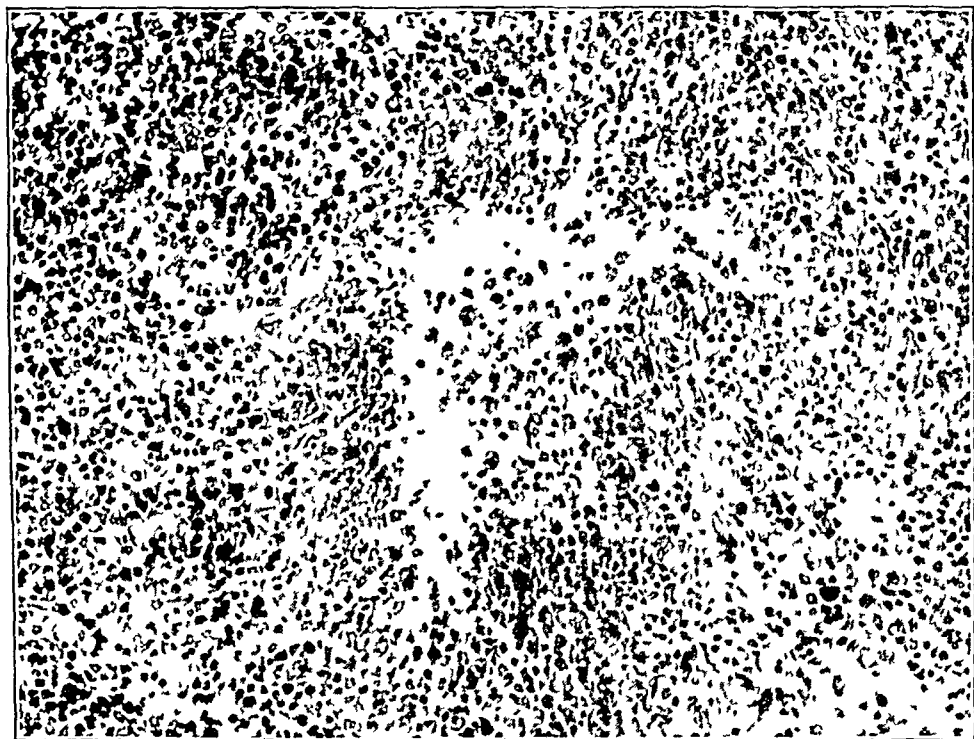


Fig 2—Stellate abscess in supraclavicular lymph node. Phloxine methylene blue, $\times 175$.

palisading arrangement and contained fragments of cellular debris. Elementary bodies were not identified. Some cells possessed two or three nuclei, but multinucleated giant cells were not encountered. The early lesions consisted of masses of large mononuclear cells in which central necrosis was either absent or just beginning. The proliferation of large mononuclear cells around the capillaries produced compression of these vessels, leading to necrosis.

In the uninvolved areas of the lymph node hyperplasia of the follicles and some proliferation of cells lining the sinuses were seen. Some areas of old fibrosis were present, but there was no relationship to the active lesions. The capsule and the surrounding tissues were not remarkable.

ISOLATION AND IDENTIFICATION OF VIRUS

The left supraclavicular lymph node was tested for the presence of the virus of lymphogranuloma venereum by a method previously described⁵. A portion of the fresh lymph node was made into a 10 per cent suspension with isotonic sodium chloride solution and lightly centrifuged. Six young adult Swiss mice of a stock free from neurotropic virus diseases were each inoculated intracerebrally with 0.03 cc of the supernatant fluid. Within three to six days all 6 mice had signs of meningoencephalitis. Two mice were killed, and the remaining 4 died within the next week. A suspension of brain from the animals which were killed was injected intracerebrally into normal mice, all of which became ill. An infectious agent so established was transmitted intracerebrally in mice for eight passages, after which transmittal was discontinued. The incubation period of the agent was two days, after which all the animals showed signs of meningoencephalitis, and the death of most of them occurred one to two weeks after inoculation. Elementary bodies similar to those of the psittacosis-lymphogranuloma venereum group of agents were found in spreads of infected mouse brains stained by the Macchiavello technic. Chick embryos were not available for this study. Bacteriologic cultures of the original lymph node and of infected animal brains on blood agar plates and in fluid thioglycollate medium showed no growth.

Of the members of the psittacosis-lymphogranuloma venereum group of agents, only three, those of lymphogranuloma, mouse pneumonitis and psittacosis (two strains) are sensitive to the sulfonamide drugs⁶. Of these three, only the agent of lymphogranuloma has been shown to infect mice by the intracerebral but not by the intraperitoneal route. The virus isolated from this patient satisfied these criteria for identification as a strain of the virus of lymphogranuloma venereum.

Tests for tissue tropisms and sulfonamide inhibition were carried out as previously described⁵. Six animals were inoculated intracerebrally with 0.03 cc of a 10 per cent suspension of infected mouse brain. All became ill in two days and died within two weeks. A similar group of

5 Wall, M. J. Isolation of the Virus of Lymphogranuloma Venereum from Twenty-Eight Patients. Relative Value of the Use of Chick Embryos and Mice, *J. Immunol.* 54: 59-64 (Sept.) 1946.

6 Hamre, D. M., and Rake, G. Feline Pneumonitis (Baker), New Member of the Lymphogranuloma-Psittacosis Group of Agents, *J. Infect. Dis.* 74: 206-211 (May-June) 1944. Meikeljohn, G., Wagner, J. C., and Beveridge, G. W. Studies on the Chemotherapy of Viruses in the Psittacosis-Lymphogranuloma Group. I. Effect of Penicillin in Sulfadiazine on Ten Strains in Chick Embryos, *J. Immunol.* 54: 1-8 (Sept.) 1946. Wiseman, R. W., Meikeljohn, G., Lackman, D. B., Wagner, J. C., and Beveridge, G. W. Studies on the Chemotherapy of Viruses in the Psittacosis-Lymphogranuloma Group. II. Effect of Penicillin and Sulfadiazine on Seven Strains in Mice, *ibid.* 54: 9-16 (Sept.) 1946.

mice were given intraperitoneal injections of 0.5 cc of the same material. None of these animals became sick or died within one month, when the experiment was terminated.

The sensitivity of the virus to sulfonamide therapy was determined as follows. Two groups of 25 normal mice were inoculated intracerebrally with 0.03 cc of a 10 per cent suspension of infected mouse brain. The mice of one group served as controls, these were given plain tap water to drink. The animals of the other group received 0.1 per cent of sulfadiazine in their drinking water from the time of inoculation. All the control animals became sick in two days and died within two weeks. All 25 of the mice treated with sulfadiazine remained well, showing no signs of illness for one month, when they were discarded.

In summary, the agent was identified as a strain of the virus of lymphogranuloma venereum because of several characteristics. These were the presence of elementary bodies, infectivity for mice when transmitted by the intracerebral route and not by the intraperitoneal route and sensitivity to sulfonamide therapy.

COMMENT

The presence of an active lymphogranuloma venereum infection in this patient was proved by the isolation of the virus from a lymph node which showed histologically characteristic lesions. The same infection probably produced the enlargement of the mediastinal lymph nodes which subsided as the patient recovered.

We believe that the pericarditis in the patient was also a manifestation of this disease. Thorough studies did not reveal any evidence of tuberculosis or rheumatic fever. The existence of a benign form of pericarditis for which the cause was not determined has recently been noted.⁷ The possibility that in some cases this condition might be caused by lymphogranuloma venereum should be considered.

Earlier studies in this clinic have shown that the histologic picture of lymphogranuloma venereum is sufficiently distinct to warrant a definite diagnosis.⁸ This case confirms our previous conclusions, since the diagnosis of lymphogranuloma venereum was first made by the histologic study of the excised lymph node. There were no clinical or other laboratory findings at that time to suggest this infection.

The high titer of complement-fixing antibodies in the serum of the patient is confirmatory evidence of an active infection with this virus.

7 Logue, R. B., and Hendkos, M. H. Acute Pericarditis of Benign Type, *Am Heart J* 36: 587-599 (Oct.) 1948.

8 Sheldon, W. H., and Heyman, A. Lymphogranuloma Venereum. A Histologic Study of the Primary Lesion, Bubonulus and Lymph Nodes in Cases Proved by Isolation of the Virus, *Am J Path* 23: 653-671 (July) 1947.

In recent studies we have found that inactive and long-standing infections of lymphogranuloma venereum usually produced antibodies in low titer⁹ None of the patients whom we have observed with other venereal diseases and preexistent lymphogranuloma venereum had titers as high as 1:640

The unusual manifestations of lymphogranuloma venereum exhibited in this patient emphasize the protean character of the disease Just as in syphilis, the clinical signs of lymphogranuloma venereum may not suggest its venereal origin, and the disease may remain unrecognized unless its systemic manifestations are kept in mind

SUMMARY

An unusual manifestation of lymphogranuloma venereum consisting of supraclavicular and mediastinal lymphadenopathy and pericarditis has been described The diagnosis in this case was first established by the histologic study of an excised lymph node A virus was isolated from the supraclavicular lymph node and identified as the agent of lymphogranuloma venereum This case emphasizes the systemic nature of lymphogranuloma venereum, the clinical manifestations of which may not suggest its venereal origin

⁹ Wall, M J , Heyman, A , and Beeson, P B Studies on the Complement Fixation Reaction in Lymphogranuloma Venereum, *Am J Syph Gonorr & Ven Dis* **31** 289-299 (May) 1947

Book Reviews

Teaching Psychotherapeutic Medicine By Walter Bauer and others Edited by Helen L. Witmer Price, \$3.75 Pp 484 New York The Commonwealth Fund, 1947

This excellent and timely volume sponsored by the Commonwealth Fund reports the details of an experimental postgraduate course in psychotherapeutic medicine. A group of well trained psychiatrists and physicians have combined their efforts in a vivid and intelligent way to help physicians better to understand their patients and the nature of their disorders. The existence of such a course stems naturally from a widespread feeling that physicians do not always know how adequately to evaluate the personal, psychologic and adjustment problems of their patients and that they may tend too much toward the diagnosis of crude organic diseases. It is of interest that many of the things brought out in this book were well known (in simpler terms) to every family physician a generation or two ago. He could hardly have practiced medicine without emphasizing these values. Now it appears to be necessary to point out to physicians that they must understand human nature and must be kind and wise and resourceful and that they should not act automatically on the basis of blood chemistry reports for some remote laboratory.

One wonders whether part of the fault does not lie in our undergraduate medical education or, indeed, even further back in the preliminary schools. Overemphasis on vocational studies and lack of emphasis on history, language and literature and those common grounds on which educated persons have always met may produce physicians who later need to be taught the elements of human relations. There is food for thought here for deans and teachers in high school, college and medical school. The book brings out, however, much more than mere basic principles, and every physician can profit from the expert discussions on the technic of psychosomatic study and on the psychotherapeutic approach to specific problems.

Blood Derivatives and Substitutes By Stanley White and Jacob J. Weinstein Price, \$7.50 Pp 484 Philadelphia The Williams & Wilkins Company, 1947

The vast wartime experiences with whole blood and blood derivatives is recorded in literally thousands of articles and armed service reports. This book serves the valuable function of assembling in one volume the many lessons learned during World War II. The majority of the technics available for the preparation of plasma, the operation of blood plasma banks and the preparation of plasma derivatives are presented in great detail. The theoretic and empiric indications for the use of plasma in therapy are discussed exhaustively. The chapter dealing with human serum albumin is complete and is a fair statement of the value of this material. The long chapter on "shock" is as likely to confuse as to enlighten the general reader. The authors have an evident preference for plasma in treatment of shock which is not shared by all authorities. They also tend to minimize the hazard of the transmission of viral hepatitis with pooled plasma. It is unfor-

fortunate that the authors have not acknowledged adequately the pioneer work of the Russians and the British. It should be recalled that blood was delivered by air to the British hospitals in the Western Desert campaigns several years before it was available in comparable amounts for American troops. The text is marred by numerous misspellings, and by editorial inconsistencies, e.g., Mgm, mgm, mg, Mu, mu, microns, ml, cc, Ångstrom, Angstrom, angstrom, Å. In spite of these, and in spite of the compendious nature of this book, it should be a useful addition to the library of any physician who uses blood derivatives and substitutes.

Arteriovenous Anastomoses in the Extremities By Thorkil Vangaard, M.D.
Copenhagen Theo Munksgaard, 1940

This is a careful, well documented study of the function of the arteriovenous anastomoses in the fingers and toes of man. These shunts are under the dual control of the central nervous system and the local thermal influence. While the arteriovenous anastomoses control the skin temperature through volume changes in the superficial venous bed, the arterioles and capillaries operate by generalized dilatation which results both in increased temperature and in redness of the skin.

Regulation of temperature is governed by two separate and distinct centers. At moderate room temperatures small variations are stabilized by the help of the shunts, which affect the caliber and regulate the heat dissipation from superficial veins. At high temperatures heat radiation is initiated by a dilatation of the skin arterioles, capillaries and small veins together with the secretion of sweat. The shunts do not seem to be dependent on the cerebral cortex for their thermoregulatory activity and are most likely governed by the hypothalamus.

This thesis is written in Danish and thus is inaccessible to most American readers. It contains an excellent bibliography and some clinical observations which bear repetition and deserve further study.

Brief Psychotherapy By Bertrand S. Frohman, M.D. Price, \$4 Pp 265 Philadelphia Lea & Febiger, 1948

This little book is extremely well written and should be of great value to the general physician, since the elementary concepts of psychiatric diagnosis and procedure are clearly stated in simple terms. It is certainly convenient to have, in a few pages, differential discussion of repression, suppression, sublimation, rationalization, overprotestation and projection. Psychotherapy is dealt with in a reasonable and sound manner, and if the book does not offer a full education in psychiatry it will without doubt help the general physician to understand the less tangible but ever more important psychologic side of medicine. There are a bibliography, a glossary of psychiatric terms and an index.

Occupational Medicine and Industrial Hygiene By Rutherford T. Johnstone, M.D. Price, \$10 Pp 604, with 117 illustrations St. Louis The C. V. Mosby Company, 1948

This book makes pleasant as well as instructive reading. It is extremely well written, and the author, in addition to knowing his subject, evidently enjoys the task of putting it clearly before his audience. There are introductory chapters on the general problems of industrial medicine followed by discussion of the disorders resulting from industrial hazards such as poisons and injuries. The concluding chapters on industrial hygiene are especially useful. Numerous excellent illustrations, and bibliographies follow each chapter.

BLOOD FIBRINOGEN IN MYOCARDIAL INFARCTION

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TWO COMPONENTS of the blood proteins, prothrombin and fibrinogen, are affected in the regeneration and destruction of tissue. Whipple and his associates¹ showed that injury to hepatic tissue or hepatectomy will reduce the fibrinogen content of the blood. On the other hand, "injury or inflammation of tissues is the most powerful stimulus to fibrinogen production."² Fibrinogen and prothrombin are essential elements required for the clotting of blood which occurs at the site of any injury.

In a previous publication, it was shown that in cases of acute myocardial infarction the prothrombin time becomes shortened.³ As the injured area heals, the clotting time returns to normal. The present investigation dealt with another of the blood proteins, the plasma fibrinogen, in an effort to determine whether similar changes occur in such cases.

MATERIALS AND METHODS

Twenty-eight patients with acute myocardial infarction were studied. Plasma fibrinogen was determined for each patient two or three times a week. Although many of the usual methods for analysis of fibrinogen are subject to error, the procedure in which the fibrin clot is digested and nesslerized is a valid and acceptable means of determination in the opinion of most biochemists.⁴ The established normal values range from 0.2 to 0.4 Gm per hundred cubic centimeters. As a check on this method, determinations were made for a normal subject for four months. During this time his values for fibrinogen varied from 0.2 to 0.3 Gm.

From the Division of Cardiology, Department of Medicine, New York Post-Graduate Medical School and Hospital.

¹ Whipple, G. W., Smith, H. P., and Belt, A. E. *Am J Physiol* 52:72, 1920.

² Everett, M. R. *Medical Biochemistry*, ed. 2, New York, Paul B. Hoeber, Inc., 1946, p. 70.

³ Meyers, L., and Poindexter, C. A. *Am Heart J* 31:27, 1946.

⁴ Hawk, P. B., and Bergeim, O. *Practical Physical Chemistry*, ed. 11, Philadelphia, P. Blakiston's Son & Co., 1937, p. 453.

RESULTS

In all instances in which a definite myocardial infarction could be demonstrated by electrocardiographic examination and clinical observation, the value for plasma fibrinogen increased. It paralleled the sedimentation rate fairly closely (chart). The more extensive the infarction, as judged by chemical and laboratory observations, the greater the amount of fibrinogen demonstrated in the blood. When the presence of an infarction was equivocal and no change was seen in the sedimentation rate, the fibrinogen level was not abnormal.

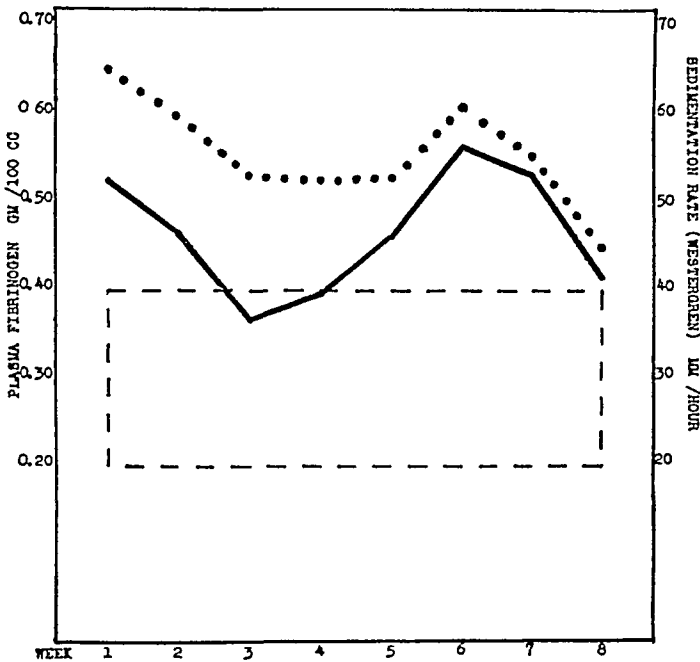


Chart showing average of weekly determinations of plasma fibrinogen and sedimentation rate. The dotted line indicates the value for fibrinogen and the unbroken line the sedimentation rate. The broken line bounds the normal range for fibrinogen. Standard deviation of values for fibrinogen was 0.06, and for the sedimentation rate it was 6.7.

The plasma fibrinogen value failed to return to normal during the period of observation for all patients who recovered. This failure to reach normalcy may be ascribed to the fact that these studies could not be pursued after the patients were discharged from the hospital. In general, however, the trend of the plasma fibrinogen level was downward at the time of discharge.

In 2 patients given dicumarol, the values for fibrinogen were maintained at an elevated level during the active phase of infarction, in spite of the increase in the prothrombin time.

CONCLUSIONS

1 Plasma fibrinogen increases at the time of the initial injury to muscle and remains elevated during the period of healing of the infarcted area

2 The classic period of five to six weeks of rest does not correspond with the cessation of healing activity of the infarction in every instance. This disparity is revealed by the presence of an increased amount of fibrinogen in the blood after that period. At times, the plasma fibrinogen may return to normal as early as three or four weeks after the infarction.

3 Fibrinogen levels roughly parallel the sedimentation rate.

4 The plasma fibrinogen is not affected by dicumarol therapy, an indication that it may be a valuable test to determine activity of the infarction even in the face of anticoagulant therapy.

This investigation indicates that in the absence of complicating factors the blood protein fractions, fibrinogen and prothrombin, may be an excellent mirror of the injury to cardiac muscle and may serve as an index of the progress of the reparative process. Subsequent investigations along these lines may disclose whether an increase in these protein fractions may so enhance the clotting power of the blood as to produce further thrombotic phenomena within and at distant points from the heart.

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TROPICAL EOSINOPHILIC ASTHMA

Report of Two Cases

ISRAEL FOND, M D

AND

PAOLO RAVENNA, M D
CHICAGO

OF THE many diseases contracted by Americans in distant countries, tropical eosinophilic asthma seems to be the least known, as only 3 cases have been reported¹ The subject of this study is a brief description of the disease and a report of 2 additional cases in which the condition had been treated as bronchial asthma for years and in which recovery occurred a few days after specific treatment with neoarsphenamine
U S P

DEFINITION

Tropical eosinophilic asthma is a disease of tropical and semitropical regions It is characterized by chronic bronchitis with nonseasonal nocturnal paroxysmal cough, with dyspnea, leukocytosis and high eosinophilia This disease has been described under various names² We suggest

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2 (a) Weingarten, R J Tropical Eosinophilia, Lancet 1 103 (Jan 23) 1943 (b) Gupta, S P Eosinophilic Lung—Report of Four Cases, J Indian M A 14 102 (Feb 3) 1945 (c) Hodes, P J, and Wood, F C Eosinophilic Lung, Am J M Sc 210 288 (Sept) 1945 (d) de Lange, C D, Anguilliosis en het ziektebeeld van de "idiopathische Hypereosinophilie," Geneesk tijdschr v Nederl - Indie 67 673, 1928, cited by van der Sar^{2h} (e) Viswanathan, R Pulmonary Eosinophilosis, Indian M Gaz 80 392 (Aug) 1945 (f) Patel, N D Benign Eosinophilia with Pulmonary Shadows, Indian Physician 4 93 (May) 1945 (g) Soysa, E, and Jayawardewa, M D S Pulmonary Acariasis A Possible Cause of Asthma, Brit M J 1 1 (Jan 6) 1945 (h) van der Sar, A Pulmonary Acariasis Its Relationship to Eosinophil Lung and Löffler's Syndrome, Am Rev Tuberc 53 440 (May) 1946

the name tropical eosinophilic asthma because it emphasizes the main morbid manifestations

HISTORY AND GEOGRAPHIC DISTRIBUTION

Tropical eosinophilic asthma was first described by Weingarten^{2a} in India in 1943. Since then it has been recognized as a common disease in that country.³ Its presence was observed in Ceylon,⁴ the East Indies,⁵ Cuba,^{2b} the Dutch West Indies,⁶ Peru⁷ and Africa.⁸ The disease has been reported in British military personnel returned from endemic areas.⁹

Its first occurrence in an American returning from overseas service was described by Hirst and McCann^{1a} and 2 additional cases were reported by Irwin^{1b}, all 3 cases included a record of military service in the south Pacific area.

ETIOLOGIC ASPECTS

The etiology is unknown. There is no relation between tropical eosinophilic asthma and syphilis,^{2a} and it is not likely that the disease may be caused by other spirochetes (bronchial spirochetosis) because penicillin has no effect on its course.

In India and other countries, mites were observed in the sputum of many patients with the disease¹⁰, in other areas microfilariae were seen in the lymph nodes of some patients¹¹ or *Strongyloides stercoralis* was found in the sputum.^{2d}

3 Gupta ^{2b} Hodes and Wood ^{2c} Viswanathan ^{2e} Patel ^{2f}

4 (a) Carter, H. F., and D'Abrera, V. St. E. Mites (Acarina). A Probable Factor in the Aetiology of Spasmodic Bronchitis and Asthma Associated with High Eosinophilia, *Tr. Roy. Soc. Trop. Med. & Hyg.* **39** 373 (April) 1946.
(b) Soysa and Jayawardena ^{2g}

5 Meyers, F. M., and Kouwenaar, W. Over hypereosinophilie en over een merkwaardige vorm van filariasis, *Geneesk. tijdschr. v. Nederl.-Indie* **79** 853 (April 4) 1939, cited by van der Sar ^{2h}

6 van der Sar, A., and Hartz, H. Syndrome, Tropical Eosinophilia and Microfilaria, *Am. J. Trop. Med.* **25** 83 (March) 1945. de Lange ^{2d} van der Sar ^{2h}

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9 Apley, J., and Grant, G. H. Tropical Eosinophilia as Seen in England, *Lancet* **1** 812 (June 30) 1945. Hunter ^{8b} Parsons-Smith ^{8c}

10 Carter, H. F., Wedd, G., and D'Abrera, V. St. E. The Occurrence of Mites (Acarina) in Human Sputum and Their Possible Significance, *Indian M. Gaz.* **79** 163 (April) 1944. Soysa and Jayawardena ^{2g} van der Sar ^{2h} Carter and D'Abrera ^{4a}

11 Meyers and Kouwenaar ⁵ van der Sar and Hartz ⁶

As one might anticipate with a tropical disease, intestinal parasites (*Ancylostoma duodenale*, *ascaris*, *Trichuris trichuria*, *Blastocystis hominis* and *Trichomonas fecalis*) were demonstrated in many patients. Yet the elimination of these infestations seems ineffective in the control of tropical eosinophilic asthma.^{2f}

CLINICAL PICTURE

The onset is gradual with malaise, low grade fever, loss of weight and paroxysmal coughing and wheezing, worse at night or the early morning. A "musical chest" and, sometimes, a palpable spleen are the only findings. After a few weeks, the temperature returns to normal, the loss of weight ceases and the spleen is no longer palpable. However, paroxysmal coughing and wheezing persist for years without much variation. The initial acute febrile stage may not always be present or recognized.

The course is chronic and is known to last several years, without appreciable changes in symptoms. Spontaneous recovery or complications have not been described.

RESULTS OF LABORATORY STUDIES

The erythrocyte count and the hemoglobin concentration are within normal limits. Leukocytosis and eosinophilia appear early and persist indefinitely. The leukocyte count may be as high as 64,000, with up to 84 per cent eosinophils.^{2a} It is of interest that the leukocytosis is caused chiefly by the increase in eosinophils (see fig. 1).

Bone marrow is generally active, with normal megakaryocytes, erythropoiesis and leukopoiesis except for a great prevalence of elements of the eosinophilic series and the presence of some large eosinophilic myelocytes and metamyelocytes.

In uncomplicated cases the Kahn reaction of the blood is negative. Results for the cold agglutination test were reported positive at levels of 1:8 to 1:1,024 in 90 per cent of cases.^{2e}

Sputum is usually scanty and seromucous. Eosinophils may be present in high percentages.

Roentgenograms of the chest in early cases show a diffuse, fine mottling of the pulmonary fields, which resembles miliary tuberculosis and disappears after three to four weeks.^{2a} In late cases, a widening of the bronchial shadows may be seen, a sign identical to that observed in chronic bronchitis and bronchial asthma. Often the roentgenographic picture of the chest is normal.

TREATMENT

In tropical eosinophilic asthma, ephedrine, epinephrine and aminophylline give only temporary relief. Specific treatment consists of the

administration of arsenicals Neoarsphenamine is given intravenously in increasing doses for a total of five injections, at five day intervals The usual schedule is 0.15, 0.30, 0.45 and 0.45 Gm Oxyphenarsine hydrochloride U S P ("mapharsen") has been used in proportionately lower doses

Oral administration of arsenicals has been employed successfully¹² Carbarsone U S P is given in doses of 0.25 Gm twice or thrice daily for a total of 5 Gm, acetarsones N F ("stovarsol") is given in the same dose The course is repeated after a ten day interval Some patients, however, failed to respond to arsenicals given orally, but recovered after treatment with neoarsphenamine¹³

The effect of treatment is prompt and typical There is an exacerbation of symptoms a few days after the beginning of treatment, and the patients complain of increased dyspnea and cough for several nights Concurrently, the leukocyte count and the number of eosinophils show a further increase In the second week of treatment the symptoms rapidly subside, with the patients feeling much better or well and able to get along without symptomatic treatment Within two or three weeks clinical recovery is complete Leukocytosis and eosinophilia decline slowly but steadily The levels return to near normal in two to four months

Recurrences (or reinfections?) were described in countries where the disease is endemic None have been reported as yet in countries where the disease is not endemic

DIAGNOSIS

Tropical eosinophilic asthma should be suspected whenever a patient who has returned from tropical regions complains of chronic paroxysmal cough with dyspnea and his blood shows leukocytosis with great eosinophilia The diagnosis is confirmed by the aggravation of symptoms when arsenic is given and the prompt recovery following completion of treatment

In the early acute stage the presence of eosinophilia will help in differentiation of the disease from miliary tuberculosis The only condition that might be confused with tropical eosinophilic asthma is the Löffler syndrome (eosinophilic pneumonopathy), because transitory pulmonary infiltrations, eosinophilia and slight fever are present in both diseases¹⁴ However, the leukocytosis is only slight or absent in Löffler's syndrome The relative eosinophilia (percentage of eosinophils in the differential count) may be equally high in both diseases, but the

12 Weingarten^{2a} Patel^{2f} Soysa and Jayawardewa^{2g} van der Sar^{2h} Carter and D'Abrera^{4a}

13 Irwin^{1b} Merino⁷ Parsons-Smith^{8c}

14 Löffler, W Die fluchtigen Lungeninfiltrate mit Eosinophilie, Schweiz med Wchnschr 66 1069 (Nov 7) 1936

absolute eosinophilia (number of eosinophils per cubic millimeter) is much greater in tropical eosinophilic asthma. The entire course of the Löffler syndrome is run in a few days, while tropical eosinophilic asthma may last for years. The Löffler syndrome is manifested by extensive roentgenographic changes and slight pulmonary signs and symptoms. The opposite is true of tropical eosinophilic asthma. Thus, Löffler's syndrome simulates pulmonary tuberculosis, while tropical eosinophilic asthma suggests bronchial asthma.

Eosinophilic leukemia is excluded on the morphologic appearance of the peripheral blood and the bone marrow and the lack of the general manifestations of leukemia.

REPORT OF CASES

CASE 1—This patient enlisted in the United States Marine Corps in 1941 at the age of 19 years. He served in the Samoa Islands for two and a half years and later in Guam. In June 1945, he reported to sick call complaining of shortness of breath which had begun shortly after his arrival in Guam. Leukocytosis (12,180 cells) with 48 per cent eosinophils was found. The roentgenogram of the chest revealed a slight accentuation of the bronchovesicular shadows bilaterally. The diagnosis of bronchial asthma was made, and symptomatic treatment was given. In December 1945, the patient was discharged from the service. He continued to have attacks of coughing and dyspnea, especially at night. However, he did not seek medical attention until May 1946, when he reported to the outpatient department of the Veterans Administration Regional Office, in Chicago, where he was given ephedrine and "amytal." In October 1946, he was transferred to the allergy clinic, where he was first seen by one of us (I. F.). He still complained of dyspnea and cough, especially at night.

His family history was not contributory and included no allergic diseases. He appeared to be a well developed, well nourished, rather pale young white man. No cyanosis or dyspnea was present. The lungs were resonant with normal respiratory sounds except for scattered musical rales which cleared on coughing. The heart showed no abnormalities.

Laboratory Findings—On November 26, the leukocyte count showed 19,000 cells per cubic millimeter, with 25 per cent neutrophils, 19 per cent lymphocytes and 56 per cent eosinophils. On several occasions thereafter the leukocyte count varied from 16,600 to 24,000, with 41 to 56 per cent eosinophils (see fig. 1). The sternal puncture performed in June 1947 (P. R.) showed normal erythropoiesis and megakaryocytes. Granulopoiesis was normal except for a great prevalence of eosinophilic cells in all stages of maturation. Many of the eosinophilic cells were larger than normal. The urine was normal, the sputum showed no acid-fast bacteria or parasites, 40 per cent of the leukocytes in the sputum were eosinophils. On repeated examinations, the stool showed no parasites, ova or protozoa. The duodenal drainage contained no parasites.

No abnormalities were seen on repeated roentgenographic examinations of the chest.

Routine cutaneous tests showed positive reaction to blackberries, shrimp, house dust, feathers, wool and cattle dander. Desensitization with house dust and catarrhal vaccine was then carried out between December 1946 and June 1947,

supplemented by the administration of ephedrine, "amytal" and epinephrine inhalations. There was no subjective or objective change in the patient's general condition until the end of June.

On June 23, 0.15 Gm of neoarsphenamine was given intravenously, followed by one injection of 0.30 Gm and three injections of 0.45 Gm at five day intervals. Two days after the administration of the second dose of neoarsphenamine, the asthma became much severer and the patient had to use epinephrine for five or six nights in succession. A last attack of asthma, slight this time, occurred on July 9. After the last injection of neoarsphenamine on July 11 he became completely asymptomatic and has remained so to the time of writing. His blood count on October 15 showed 7,600 leukocytes with 5 per cent eosinophils.

Figure 1 represents a summary of significant observations in this case.

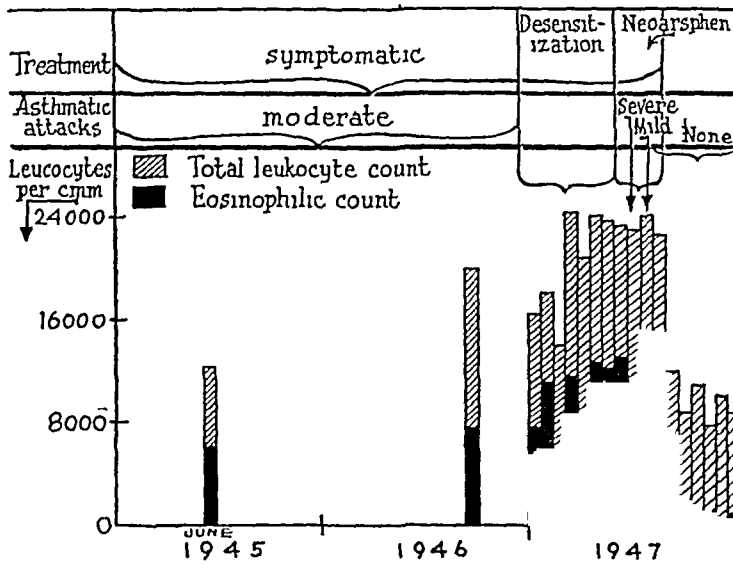


Fig 1—Chart summarizing significant observations on a patient (case 1) with tropical eosinophilic asthma.

CASE 2—The patient enlisted in the United States Marine Corps in January 1942 at 22 years of age. He served in the Samoa Islands for sixteen months, then in other islands of the south Pacific and in Hawaii. In July 1944, he landed in Guam and two weeks later he began to complain of cough and dyspnea in the evening and during the night. Leukocytosis (18,800 cells), with 26 per cent eosinophils, was recorded. The roentgenogram of the chest was interpreted as showing nothing abnormal. A diagnosis of bronchial asthma was made. After prolonged hospitalization in various naval medical installations, the patient was separated from the service in June 1945.

After discharge he continued to cough and wheeze, especially at night. He used a patent medicine for relief of his "asthmatic attacks." In December 1946, he reported to the outpatient department of the Chicago Regional Office of the Veterans Administration, where he was first seen by one of us (I. F.).

He gave a history of hay fever and asthma on both paternal and maternal sides. On physical examination he appeared as a well developed, well nourished white man. The pulse, temperature and respiratory rate were normal. The configuration and expansion of the chest were normal. The lungs were resonant, and the respiratory sounds were normal. No wheezes or rales were heard at the time of

the first examination but were noticed repeatedly on subsequent visits to the clinic

Results of Laboratory Studies—In December 1946, the leukocyte count was 11,500, with 54 per cent neutrophils, 13 per cent lymphocytes and 33 per cent eosinophils. Several blood counts between that date and the end of June 1947 showed a variation in the leukocyte count of 14,000 to 18,000 cells, with 15 to 37 per cent eosinophils. The sternal puncture performed at the end of June 1947 (P. R.) revealed no abnormality except for deviation of granulopoiesis toward the eosinophilic series, with many eosinophilic myelocytes and metamyelocytes. Giant eosinophilic myelocytes were occasionally encountered. Some eosinophilic cells had relatively few granules.

The electrocardiogram and the basal metabolic rate were within normal limits. No abnormalities were demonstrated in the urine or in the sputum, except

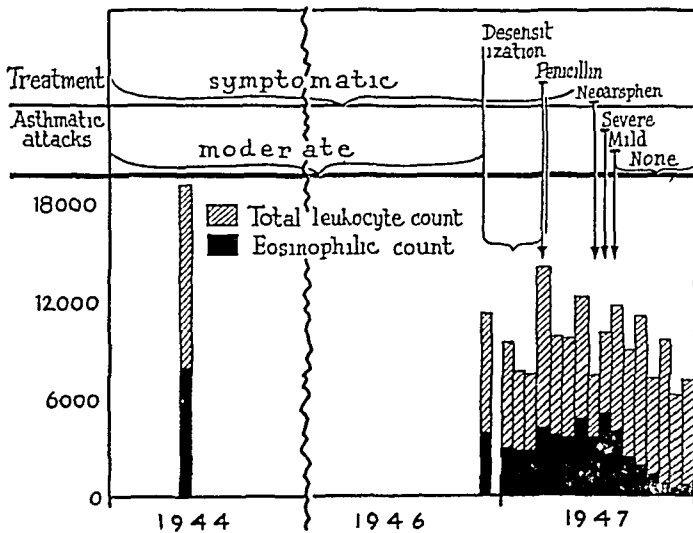


Fig. 2—Chart summarizing data on a patient (case 2) with tropical eosinophilic asthma

that the latter showed up to 40 per cent eosinophils. Repeated examinations of the feces and of the duodenal drainage manifested no parasites, protozoa or eggs. On several occasions the roentgenograms of the chest were reported normal.

Intradermal tests gave positive reactions to house dust, feathers, wheat, kidney beans, garlic, yeast, wool, buckwheat and rice. Desensitization was then carried out between January and June 1947 and was supplemented by the administration of ephedrine and "amytal" and the elimination of foods to which the patient showed positive cutaneous reactions. However, the patient continued to have nocturnal asthmatic attacks.

Between July 1 and July 5, 2,400,000 units of penicillin was administered in doses of 300,000 units (Romanski formula) twice daily. There was no immediate aggravation of symptoms nor any change in the blood picture. The patient stated he felt a little better for a few days, but by July 25 his condition was the same as before. Then neoarsphenamine was given in a dose of 0.15 Gm., followed by one of 0.30 Gm. and three injections of 0.45 Gm. each, at five day intervals. On August 13 the last dose was given. The institution of arsenical treatment was followed by an aggravation of symptoms lasting a few days. After the

treatment, was completed, the patient became completely asymptomatic, and when last seen, in January 1948, he was well and his leukocyte count was 7,250, with 9 per cent eosinophils

Figure 2 shows the salient features of this case

COMMENT

The cases reported represent typical examples of tropical eosinophilic asthma, showing the long duration and ease of confusion with bronchial asthma, in both cases the latter diagnosis had been made by various physicians in different hospitals and clinics throughout treatment. In neither case was there a history of acute febrile onset.

It cannot be decided whether tropical eosinophilic asthma should be considered as a single disease or as a syndrome caused by various etiologic agents. The specific response to arsenicals suggests a single etiologic agent, though of the many parasites so far recorded in these cases none is known to be destroyed by arsenicals.

It is possible that arsenic may not act as an anti-infective drug but may directly depress the eosinophilia, as solution of potassium arsenite does in cases of leukemia. If this assumption is made, the aggravation that accompanies the commencement of treatment with arsenicals might then be caused by a massive destruction of eosinophils with release of histamine (in which the eosinophils are particularly rich). However, we feel that the theory is not convincing, because the amount of arsenicals employed in the treatment of tropical eosinophilic asthma is small and the complete recovery precedes by months the return of the leukocyte count to normal.

The relation of tropical eosinophilic asthma with the Löffler syndrome merits further attention because the conditions have something in common, namely, the eosinophilia associated with respiratory disease, and the fact that infestations with various parasites were recorded in both diseases.¹⁵ It may be of interest to see whether Löffler's syndrome is influenced by arsenical treatment.

These are only a few of the many problems that should stimulate further investigation in the field of asthma.

SUMMARY AND CONCLUSIONS

Tropical eosinophilic asthma is a chronic disease manifested by paroxysmal cough, dyspnea, massive eosinophilia and prompt response to treatment with arsenicals administered parenterally or by mouth.

¹⁵ Hoff, A., and Hicks, H. M. Transient Pulmonary Infiltration. A Case with Eosinophilia (Löffler's Syndrome) Associated with Amebiasis, *Am Rev Tuberc* 45 194 (Feb.) 1942. Wright, D. O., and Gold, E. M. Löffler's Syndrome Associated with Creeping Eruption (Cutaneous Helminthiasis), *J A M A* 128 1082 (Aug. 11) 1945.

In this country, 5 cases of tropical eosinophilic asthma have been recorded, all in United States military personnel returned from the south Pacific area. This disease will probably be recognized outside the veteran population, because it is endemic in Cuba and other Caribbean islands.

It is suggested that all cases of bronchial asthma associated with unexplained high eosinophilia be given a therapeutic trial with arsenicals, since tropical eosinophilic asthma may not be as rare in this country as it appears from the available reports in the literature.

NOTE—Since this report was submitted for publication an additional case of tropical eosinophilic asthma has come to our attention. The leukocyte count was 20,700, with 43 per cent eosinophils. Treatment consisted of five injections of oxyphenarsine hydrochloride U S P. Three years later the patient was reexamined by us and he was well. The leukocyte and differential counts had returned to normal.

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ORTHOSTATIC INFLUENCES ON THE DISTRIBUTION OF ATHEROMATOUS LESIONS IN THE CEREBRAL AND OTHER ARTERIES

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ATHEROSCLEROTIC lesions containing intimal deposits of lipid or calcium occur characteristically only in those portions of the vascular system in which the blood pressure ordinarily is relatively high. Fibrous intimal thickenings sometimes found in sclerotic veins rarely contain either of these materials. Intimal lipid deposits are seldom found in the pulmonary arteries or in very small systemic arteries unless the blood pressure in these areas has been abnormally high. Lesions analogous to atheromatous plaques of arteries may form in the endocardium but only in those portions in which a high level of intracardiac pressure normally is developed, for example, in the aortic valve or the ventricular aspect of the anterior mitral valve leaflet. In coarctation of the isthmus of the aorta, atheromatous plaques are common proximal to and uncommon distal to the point of narrowing.

These well established observations suggest that a threshold of hydrostatic pressure may exist below which lipid-containing substances in colloidal form fail to penetrate the lining membrane of the vascular system. This threshold value must be considerably above the normal systolic pressure in the pulmonary arteries and somewhat below the normal systolic pressure of 120 to 130 mm. of mercury in the main systemic arteries. Above this hypothetical pressure threshold, the rate of penetration of lipid-containing substances may be directly proportional to the blood pressure since there is abundant evidence that hypertension facilitates the formation of atherosclerotic lesions.

The simplest, if not the most obvious, explanation for the manner in which blood pressure may promote the entrance of lipid-containing substances into the arterial intima is that it provides a positive filtration pressure against a permeable endothelial surface. Two features of the atherosclerotic process are difficult to reconcile with this simple explanation. The lesions are discrete or focal in character, and, secondly, they

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are distributed unequally in various arteries throughout the body. If simple filtration of substances through the intimal surface impelled by the force of intra-arterial tension is the mechanism involved, one should expect (1) diffuse, uniform deposition of lipid or other substances and (2) equal involvement of all arteries by the process, since the blood pressure is generally stated to be fairly uniform in all the major arteries.

An adequate explanation has been advanced for the collection of lipid, originally introduced into the intima in uniformly dispersed form, into discrete, localized deposits.¹ This explanation supposes that through the impetus of the constant pulsations there is a gradual displacement of such lipid from the more mobile portions of the vessel until it converges on and collects at such intimal barriers as points of branching or the most firmly anchored and therefore least mobile portions of the artery wall. Furthermore, during periods of active resorption, lipid is probably withdrawn more rapidly from the more mobile areas. This explanation is supported by the observation that intimal plaques do, in fact, develop most frequently in the aorta at points of relative inelasticity and rigid attachment.¹ A number of other observers² have noted that plaques are most often found at securely anchored portions of other arteries. Moschowitz,³ in particular, has stressed this finding.

Experimentally, this explanation has received additional support since it has been noted that in rabbits fed cholesterol this substance tends to concentrate at points in the arterial system that have been rendered immobile by the external application of silver cuffs.⁴ While there is no direct proof that intrainimal convergence of lipid occurs, in no other fashion is it possible to relate long intimal streaks of lipid to the subsequent development of discrete plaques. According to the theory of intrainimal movement of lipid to immobile areas, such streaks represent deposits in the active process of coalescence and convergence.

If the role of blood pressure in the pathogenesis of arteriosclerosis is to cause transudation into the intima of materials from which the deposits in atheromatous plaques are subsequently derived, it is necessary to

1 Wilens, S. L. The Post Mortem Elasticity of the Adult Human Aorta. Its Relation to Age and to the Distribution of Intimal Atheromas, *Am J Path* **13** 811-833, 1937.

2 (a) Lauda, E. Physiologische Druckschädigungen und Arteriosklerose der Duralgefasse, *Beitr z path Anat u z allg Path* **58** 180-184, 1921. (b) Dow, D. R. The Incidence of Arteriosclerosis in the Arteries of the Body, *Brit M J* **2** 162-163, 1925. (c) Moschowitz, E. The Cause of Arteriosclerosis, *Am J M Sc* **178** 244-267, 1929.

3 Moschowitz, E. *Vascular Sclerosis with Special Reference to Arteriosclerosis*, New York, Oxford University Press, 1942, pp 129 and 130.

4 Wilens, S. L. The Distribution of Initial Atheromatous Lesions in the Arteries of Rabbits on High Cholesterol Diets, *Am J Path* **18** 63-77, 1942.

account for the unequal involvement of different arteries. It is the purpose of this report to suggest an explanation for this phenomenon.

THE INFLUENCE OF BODY POSITION ON ARTERIAL BLOOD PRESSURE

In recumbent positions of the body the major arteries constitute a horizontal system of tubes. The blood pressure throughout such a horizontal system does not vary greatly. In standing or sitting positions, however, the major arteries become vertical systems of tubes in which the force of gravity must influence the blood pressure level developed by the force of ventricular contraction. The pressure resulting from the force of gravity may be of considerable magnitude. For example, the hydrostatic pressure at the bottom of an open vertical tube equal in length to a person 68 inches (173 cm) tall is about 110 mm of mercury, or almost as great as that developed by left ventricular contraction. The influence of gravity on blood pressure in various arteries is generally ignored. One reason for this is that most blood pressures are recorded from the brachial artery, at which point the position of the body does not greatly influence the measurements obtained.

The effect of gravity on arterial blood flow is partly neutralized by a complex series of adjustments in circulation that occurs on changing body position. This includes alterations in arteriolar constriction or dilation and in heart rate. These compensatory mechanisms maintain an adequate blood flow to the head and neck and prevent excessive blood flow to the dependent parts in the upright position. They may lessen the influence of gravity on arterial blood pressure but only to a slight extent. As long ago as 1895 Hill⁵ noted that in dogs placed in upright positions the blood pressure in the femoral artery was much higher than that in the carotid artery. The evidence available indicates that this is also true in man. Best and Taylor⁶ stated that the systolic blood pressure in the posterior tibial artery increases from 110 to 165 mm of mercury on changing from the horizontal to the vertical position. Loman, Dameshek, Myerson and Goldman⁷ have recorded carotid and femoral arterial pressures by direct puncture in both recumbent and upright positions. They found a persistent, constant rise in femoral arterial pressure averaging 31 mm of mercury and a persistent, constant fall in carotid arterial

5 Hill, L. The Influence of the Force of Gravity on the Circulation of the Blood, *J. Physiol.* **18** 15-53, 1895.

6 Best, C. H., and Taylor, N. B. *The Physiological Basis of Medical Practice*, ed 4, Baltimore, Williams & Wilkins Company, 1945, p. 140.

7 Loman, J., Dameshek, W., Myerson, A., and Goldman, D. Effects of Alteration in Posture on the Intra-arterial Blood Pressure in Man. I. Pressure in the Carotid, Brachial and Femoral Arteries in Normal Subjects, *Arch. Neurol. & Psychiat.* **35** 1216-1224 (June) 1936.

pressure averaging 23 mm in the head up position. Although the amount of change in blood pressure with alterations in position varied in different persons, it was within limits that might be attributed to the force of gravity.

In addition to altered dynamics of blood flow, there are probably other factors that temper the effect of gravity on blood pressure in individual arteries in the standing position. Pressure changes are probably not transmitted fully into extremely minute vessels or into branches that arise at sharp angles from main arteries. The formation of intimal plaques at the orifices of arteries may eventually reduce the influence of gravity on blood pressure in the further course of the vessel.

The observations of Clark, Hooker and Weed⁸ on pressure relationships within closed fluid systems with rigid or elastic walls placed in vertical or horizontal positions indicate that the elastic tissue of arteries must play an important role in this regard. They noted that when a closed system of tubes containing fluid was placed upright a level in this system could be found above which the pressure was less and below which it was greater than in the horizontal position. This level they designated as the "point of reference." In closed fluid-filled systems with elastic walls the "point of reference" was situated at a higher level than in a system with rigid, unyielding walls. This finding suggests that one of the effects of arterial elastic tissue is to limit the fall in arterial blood pressure in the upper part of the body in the standing position. It may further be supposed that with advancing age and impairment of arterial elasticity alterations in blood pressure in the various arteries on standing may become greater in magnitude. Loman, Dameshek, Myerson and Goldman^{8a} observed a greater persistent fall in pressure in the carotid artery in the head up position in persons with arteriosclerosis than in normal persons.

The influence of gravity on blood pressure in standing or sitting positions may therefore be variable in degree depending on alterations in blood flow, arterial structure and elasticity. Nevertheless, the direct measurements of Loman, Dameshek, Myerson and Goldman⁷ indicate that it is never completely abolished. The average person spends two thirds of each day in sitting or standing positions. One may conclude therefore that the arterial blood pressure is not usually uniform but is relatively high in the dependent portions and low in the superior portions of the arterial system.

8 Clark, J. H., Hooker, D. R., and Weed, L. H. The Hydrostatic Factor in Venous Pressure Measurements, *Am J Physiol* 109 166-177, 1934.

RELATIONSHIP OF DISTRIBUTION OF ATHEROMATOUS LESIONS TO
ARTERIAL BLOOD PRESSURE IN THE UPRIGHT POSITION

If the rate of formation of atherosclerotic plaques increases with the blood pressure, the arteries in the lower portions of these vertical systems should be more extensively involved than those in the upper portions. It is conceded that at necropsy in individual instances atherosclerotic plaques appear to be dispersed at random and without pattern. Yet in any group of necropsies plaques are found more frequently, abundantly and consistently in certain arteries than in others. The distribution of atherosclerosis in various arteries as described by Dow^{2b} conforms in the main with the general experience of others.

Analysis of the distribution of these lesions reveals, with the exception of the coronary and cerebral arteries, a remarkable coincidence. Intimal plaque formation is common in the inferior and uncommon in the superior parts of the arterial systems as disposed in upright positions. Thus plaque formation is more common in the lower abdominal portion of the aorta than in the descending thoracic portion, more common in the iliac than in the subclavian or carotid arteries, more common in the femoral than in the axillary or brachial arteries and more common in the tibial and peroneal than in the radial arteries. There is probably relatively little orthostatic effect on coronary arterial blood pressure since these vessels are situated fairly close to the hypothetical "point of reference" in the upright position. Other factors must be primarily concerned in the frequent involvement of these arteries by atherosclerosis.

RELATIONSHIP OF INTRACRANIAL CEREBROSPINAL FLUID PRESSURE TO
CEREBRAL ARTERIAL BLOOD PRESSURE IN THE UPRIGHT POSITION

The blood pressure in the cerebral arteries should be considerably lower in the standing than in the recumbent position. Yet these arteries, as is well known, are frequently altered by atherosclerosis. This exception would appear to invalidate any explanation for the distribution of atherosclerotic lesions based on the existence of a gradient of arterial pressure due to the force of gravity.

There is, however, one distinctive feature about the main cerebral arteries. They are situated in the pia arachnoid membranes in an external fluid environment that is itself subject to considerable fluctuations in pressure in different body positions. According to Loman, Myerson and Goldman,⁹ the pressure of cerebrospinal fluid in the cisterna magna decreases by 450 to 550 mm. of water when the body is moved from the

⁹ Loman, J., Myerson, A., and Goldman, D. Effects of Alterations in Posture on the Cerebrospinal Fluid Pressure, *Arch Neurol & Psychiat* 33 1279-1295 (June) 1935.

recumbent to the upright sitting position. At the same time the pressure in the lumbar region is correspondingly increased. In 7 of 13 persons a negative cerebrospinal fluid pressure was found in the cisterna magna with the spinal column upright. Best and Taylor¹⁰ state that in the vertical position the pressure of cerebrospinal fluid is zero in the mid dorsal region and is below atmospheric pressure above this level. These changes in pressure are obviously to a large extent gravitational effects.

The length of the column of cerebrospinal fluid from the base of the brain to the first sacral vertebra in the adult measures from 50 to 70 cm, or the equivalent in pressure of 35 to 44 mm of mercury. The column of arterial blood from the heart to the base of the brain is only 20 to 32 cm in length, or the equivalent in pressure of 12 to 20 mm of mercury. However, the "point of reference" in the vertically disposed arterial system extending from head to foot is probably somewhat below the level of the heart and this would lead to a greater fall in cerebral arterial blood pressure. Actual measurements of intracranial cerebral arterial pressure in man in the upright position are not available, but some indication of its range is obtained from the data of Loman, Dameshek, Myerson and Goldman.⁷ When the upright position was assumed, a mean fall of 23 mm of mercury in carotid arterial pressure at a point roughly two thirds to three fourths the distance from the heart to the base of the brain was found. The mean fall in cerebral arterial pressure in the vertical position due to gravity is therefore probably around 30 mm.

Thus it is seen that the fall in cerebrospinal fluid pressure outside the cerebral arteries almost invariably equals and usually exceeds the fall of blood pressure within these arteries when a change is made from the recumbent to the upright position. Cerebral arterial pressure in the latter position may be low in comparison to the arterial blood pressure elsewhere, but it is often proportionately increased in relation to its own environment within the cranial cavity because of the decrease in cerebrospinal fluid pressure. A thick unyielding arterial wall might act as an effective barrier against the differences in pressure within and without the vessel. The cerebral arteries are, however, unusually thin walled compared with other arteries. They are so thin walled, in fact, that intimal deposits of lipid are readily visible through the adventitia.

RELATIONSHIP OF INTRACRANIAL CEREBROSPINAL FLUID AND CEREBRAL ARTERIAL BLOOD PRESSURE TO CEREBRAL ARTERIAL ATHEROSCLEROSIS

Although the circumstances are different in the case of the cerebral arteries, the net result is the same as in other arteries. In sitting or standing positions the effective cerebral arterial pressure is generally increased

¹⁰ Best and Taylor,⁶ p. 935

rather than decreased because of the reduced cerebrospinal fluid pressure. If filtration of lipid-containing fluids through the intimal surfaces, impelled by hydrostatic pressure, is the initial source of the ultimate atheromatous deposits, then the cerebral arteries should be and are favored sites for atherosclerotic change.

The degree of atherosclerosis in the cerebral arteries is more often at variance with that observed in the rest of the arterial system than is the case with any other single group of systemic arteries. Not infrequently atherosclerosis may be extreme throughout the body but absent in the cerebral arteries. Severe cerebral atherosclerosis not uncommonly occurs without significant involvement of any other artery. Neuberger¹¹ has stressed the disproportionate degrees of involvement of the cerebral arteries in atherosclerosis as compared to that of other systemic arteries.

TABLE 1—*Comparison of Sex Incidence of Cerebral Infarction or Hemorrhage and Myocardial Infarction*

Lesion	Men		Women		Ratio Men/Women	Adjusted Ratios ^a Men/Women
	No	%	No	%		
Cerebral hemorrhage or infarction	195	59.2	134	40.8	1.46:1	0.65:1
Myocardial infarction	309	77.1	92	22.9	3.36:1	1.51:1
Total	504	69.0	226	31.0	2.23:1	1.0:1

^a The ratios were adjusted according to number of men and women in combined series of patients with cerebral and cardiac lesions.

Sometimes the extracranial portions of carotid arteries remain free of atherosclerotic change even though the intracranial branches are markedly sclerotic. These peculiarities of cerebral atherosclerosis suggest that the conditions necessary for its development may be different from those in other arteries.

The relative lengths of the cerebrospinal canal and the various portions of the arterial system vary considerably in different persons depending on body configuration. In general, the cerebrospinal column is long in comparison to the arterial system in persons with a long trunk and a short head and neck and extremities. In persons with a short trunk and a long head and neck and extremities the conditions are reversed. If a disproportion in the fall between intracranial cerebrospinal fluid and cerebral arterial blood pressures in the vertical position is concerned in the pathogenesis of cerebral arterial atherosclerosis, then the incidence of this lesion should be influenced by body build. Persons with long spinal columns and short head and neck and extremities should be particularly sus-

11 Neuberger, K., Arteriosclerosis, in Bumke, O. *Handbuch der Geisteskrankheiten*, Berlin, Julius Springer, 1930, pt. 7, pp. 570-636.

ceptible to cerebral atherosclerosis. Persons with a short trunk and long head and neck and extremities should be resistant. Some clinicians believe that cerebral hemorrhage or infarction is particularly common in persons of thick-set, portly configuration. Indeed Fishberg¹² states that this body build has been referred to as "status apoplecticus."

THE SEX INCIDENCE OF CEREBRAL HEMORRHAGE OR INFARCTION
COMPARED WITH THAT OF MYOCARDIAL INFARCTION AND
ITS RELATIONSHIP TO BODY MEASUREMENTS

It is well established that myocardial infarction is much more common in men than in women. Spontaneous cerebral hemorrhage or infarction is only slightly more common in white men than in white women and is less common in Negro men than in Negro women.¹³ A more precise comparison of the sex incidence of cerebral and myocardial lesions caused by arteriosclerosis is furnished in table 1. Of 329 persons with spontaneous cerebral hemorrhage or infarction at consecutive necropsies at Bellevue Hospital, New York, 195, or 59.2 per cent, were males. Of 401 persons with myocardial infarction at consecutive necropsies, 309, or 77.1 per cent, were males. Thus the cerebral lesions are only one and a half times as common in men as in women whereas the cardiac lesion is almost three and a half times as common. These ratios are distorted by the circumstance that from two to three times as many men as women are examined at necropsy in Bellevue Hospital. If the ratios are adjusted according to the proportion of men and women in the combined series of cerebral and cardiac lesions as in table 1, a more accurate comparison of the actual sex incidence is obtained. The adjusted ratios indicate that cerebrovascular lesions are more common in women than in men. For every 10 women there are only 7 men with cerebral hemorrhage or infarction, but for every 10 women with myocardial infarction there are 15 men with a similar lesion.

The differences in sex incidence of cerebral lesions due to atherosclerosis can be accounted for on the basis of differences in body build. Although there is much individual variation, the head, neck, arms and legs are relatively shorter in proportion to the thorax and abdomen in the average woman than in the average man. For example, in 50 women the mean distance from the aortic valve to the base of the brain was 23.6 cm and in 100 men it was 27.6 cm. In the same group the mean length of the

12 Fishberg, A. M. *Hypertension and Nephritis*, ed. 4, Philadelphia, Lea & Febiger, 1940, p. 660.

13 Dublin, L. I., and Lotka, A. J. *Twenty-Five Years of Health Progress: A Study of the Mortality Experience Among the Industrial Policy Holders of the Metropolitan Life Insurance Company 1911 to 1935*, New York, Metropolitan Life Insurance Company, 1937, pp. 274, 302 and 307.

spinal column from the base of the brain to the first sacral vertebra was 57.7 cm for women and 62.7 cm for men. It is thus seen that the length of the spinal canal is two and a half times as great in women and only two and a quarter times as great in men as the heart to brain measurement. The measurements of Draper¹⁴ and of Wolff and Steggerda¹⁵ indicate that the limbs of the average man are proportionately longer than those of the average woman. Compilations from Draper's data reveal that the average man is 11.1 cm taller than the average woman and that 7.1 cm of this difference is due to longer leg length. If computed in

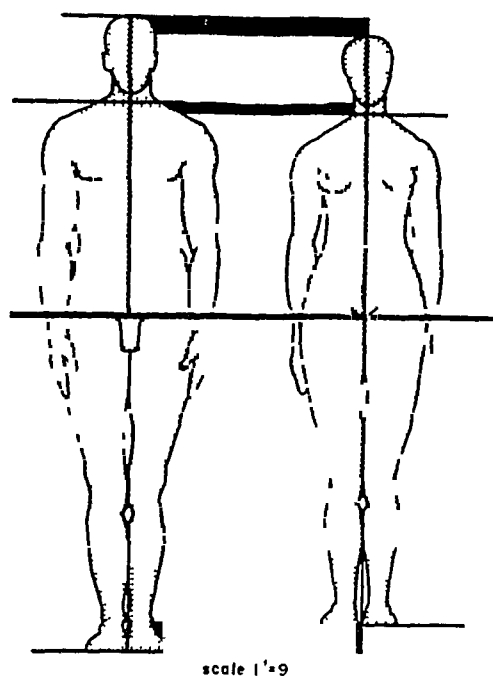


Fig. 1—Comparison of average body measurements in men and women. The length of the head and neck (solid cross bar at top) and of the legs (solid cross bar at bottom) in men exceeds that of the trunk (narrow cross bar at neck and shoulder level). The trunk, therefore, is shorter in proportion to the rest of the body in men than in women.

terms of ratios of leg and arm length to trunk length, the following results are obtained. The ratio of average arm to average trunk length in men is 1.29:1 and in women 1.21:1. The ratio of the average leg length to trunk length is 1.59:1 in men and 1.54:1 in women. Comparison of the proportions of these parts of the body in men and in women is shown graphically in figure 1. These mean differences in body configuration suggest that in the average woman there is a relatively small drop in

14 Draper, G. *Human Constitution: A Consideration of Its Relationship to Disease*, Philadelphia, W. B. Saunders Company, 1924, p. 331.

15 Wolff, G., and Steggerda, M. *Female-Male Index of Body Build in Negroes and Whites: An Interpretation of Anatomical Sex Differences*, *Human Biol.* 15: 127-152, 1943.

cerebral arterial pressure and a relatively large fall in intracranial cerebrospinal fluid pressure in the upright position. This indicates that the effective cerebral arterial pressure may be higher in the average woman than in the average man. All other things being equal, cerebral arterial atherosclerosis should be more prone to develop in the average woman than in the average man. This conforms to the sex incidence of lesions of the brain already cited.

INCIDENCE OF ATHEROSCLEROSIS OF CEREBRAL ARTERIES AND
OF CORONARY ARTERIES AND RELATIONSHIP TO
BODY MEASUREMENTS

If the explanation advanced to account for the frequent involvement of the cerebral arteries by atherosclerosis is valid, a direct relationship

TABLE 2—*Correlation Between Body Measurements and Severity of Cerebral as Compared with Coronary Arterial Atherosclerosis*

Ratio of Spinal Column Length to Heart to Brain Distance	DEGREE OF ATHEROSCLEROSIS					
	More Extensive in Cerebral Arteries		About Equal in Both Arteries		More Extensive in Coronary Arteries	
	No	%	No	%	No	%
Up to 2 20 1	2	4.9	3	7.3	36	87.8
2 20 1 to 2 40 1	6	11.5	12	23.1	34	65.4
2 40 1 and over	16	30.8	18	34.6	18	34.6
Total	24	16.5	33	22.8	88	60.7

between body build and the degree of atherosclerotic change in these vessels should be demonstrable. Accordingly, measurements were taken at necropsy of the length of the spinal canal and of the distance from heart to brain in 145 adults over 40 years of age. With the head and body horizontal and supine, the distance from the eyes to the third costochondral junction was taken as the length from the base of the brain to the aortic valve. Similarly, the distance from the eyes to the intervertebral disk between the fifth lumbar and first sacral vertebrae was taken as the length of the spinal canal. The degree of atherosclerosis in all major coronary arteries was compared to that in the cerebral arteries and the circle of Willis in each instance. The pia arachnoid over the sylvian fissure was incised in order to inspect the middle cerebral branches. Both the extent and the character of intimal plaques were noted. The process was graded as being (a) more marked in the cerebral arteries, (b) about equal in both groups of vessels and (c) more pronounced in the coronary arteries.

A definite correlation was found between the body measurements expressed as a ratio of spinal column length to heart to brain length and the relative degree of involvement by atherosclerosis of the cerebral

arteries as compared with that of the coronary arteries (table 2) Among 41 persons who had a relatively short spinal cord and a relatively long heart to brain length (ratio up to 2 20 1), in 36 the cerebral atherosclerosis was less severe than the coronary atherosclerosis On the other hand, of 52 persons with relatively long spinal columns and relatively short heart to brain length (ratio of 2 40 1 or greater), 34 had either more severe cerebral atherosclerosis or an equal degree of involvement of both groups of arteries The group of 52 persons with intermediate body measurements (ratio of 2 20 to 2 40 1) had intermediate degrees of

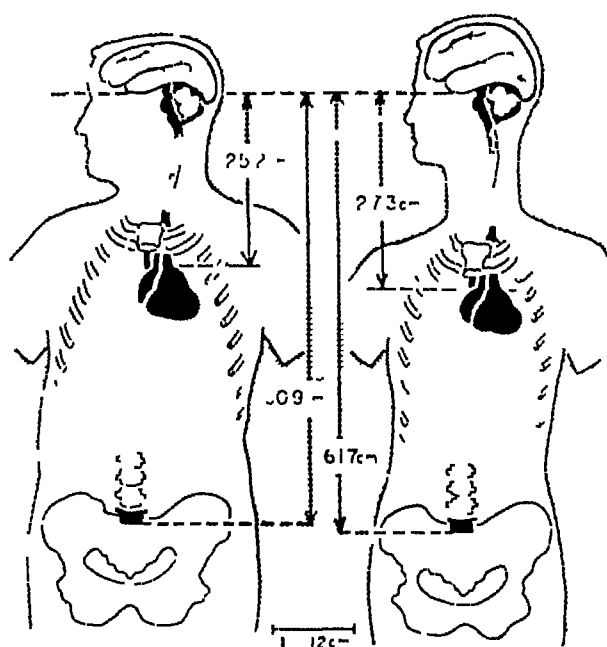


Fig 2—Relation of body build to cerebral arterial atherosclerosis The figure on the left is constructed on the basis of mean body measurements (table 3) of the group in which cerebral arterial atherosclerosis was more severe or just as severe as coronary arterial atherosclerosis The figure on the right is based on the mean body measurements of those in whom cerebral arterial atherosclerosis was less severe than coronary arterial atherosclerosis

atherosclerotic involvement of the cerebral arteries as compared with the involvement of the coronary arteries (table 2)

This correlation between body measurements and the comparative degree of cerebral and coronary atherosclerosis is independent of sex (table 3) when mean lengths of heart to brain and of spinal column are shown The ratio of spinal column length to heart to brain length is greater in men (2 37 1) and women (2 52 1) with extensive cerebral arterial lesions than it is in men (2 23 1) and women (2 41 1) with rela-

tively slight cerebral atherosclerosis The tendency of cerebral atherosclerosis to develop in women more commonly than coronary atherosclerosis is also indicated Fifty-seven per cent of the women but only 33 per cent of the men in the series had cerebral atherosclerosis that was as severe or more so than the coronary atherosclerosis

In figure 2 the short-necked, thick torso of the person with a predisposition toward cerebral atherosclerosis is contrasted with the torso of the slender, long-necked person in whom this lesion is uncommon The construction of these figures is based on the combined mean body measurements for both sexes shown in table 3

COMMENT

The simple premise on which the foregoing study is based is that in the upright position the blood pressure is unequal in the various arteries and that the amount of atherosclerotic change in any one artery of a given person varies directly with the level of blood pressure in that artery It is admitted that the evidence to support this explanation is indirect and

TABLE 3—*Correlation Between the Comparative Severity of Cerebral and Coronary Atherosclerosis and Mean Body Measurements*

Degree of Atherosclerosis	Group	No	Measurements		Ratio of Spinal Column Length to Heart to Brain Length
			Heart to Brain Mean Length Cm	Spinal Column Mean Length Cm	
Cerebral atherosclerosis more severe or equal to coronary atherosclerosis	Men	36	26 5	62 7	2 37 1
	Women	21	23 0	58 0	2 52 1
	Total	57	25 2	60 9	2 42 1
Coronary atherosclerosis more severe than cerebral atherosclerosis	Men	72	28 2	62 8	2 23 1
	Women	16	23 4	56 4	2 41 1
	Total	88	27 3	61 7	2 26 1

inconclusive Yet, in itself, this hypothesis is both reasonable and plausible By its use what otherwise appears to be a disorganized and meaningless scattering of intimal lesions becomes resolved into a definite, fairly predictable pattern

By using this hypothesis, it is possible to explain many of the well recognized peculiarities in distribution of atherosclerotic lesions The involvement of the arteries in the lower extremities is so frequent that this, in itself, suggests that the dependent portions of the body are particularly susceptible to this lesion It is the relatively high incidence of atherosclerosis of the cerebral and coronary arteries that has obscured an otherwise obvious relationship between atherosclerosis and the level of arterial blood pressure attained in the upright position The foregoing analysis, however, suggests that in spite of location in the body, the blood pressure of the cerebral arteries may be relatively increased in the upright

position. Acceptance of this theory makes it possible to explain such phenomena as the relatively high incidence of cerebral atherosclerosis in women, and, in general, to relate the high degree of involvement of these vessels to body conformation.

The importance, however, of the existence of a gradient of arterial blood pressure in the upright position is in its implications concerning the pathogenesis of atherosclerosis. Anitschkow¹⁶ believed, from his observations on the production of atheromatous lesions in cholesterol-fed, hyperlipemic rabbits, that there is normally a continuous passage of fluid from the blood into the arterial intima and that intimal lipid deposits develop when this fluid contains abnormally large amounts of cholesterol. It is generally conceded that the intimal lipid deposits in the arteries of man, because of their character and amount, are derived from the blood, but the mode of entrance and the mechanism of deposition have not been clearly established.

Among the objections that have been raised to Anitschkow's views is the fact that deposits are focal and unevenly distributed. It has been assumed therefore that local injury to certain arteries or parts of arteries must precede the entrance of lipid into the intima. In a recent review, Hueper¹⁷ lists numerous types of injuries or alterations that have been described as preceding plaque formation and also a wide variety of injurious agents that are said to act selectively on arterial walls.

If the explanations advanced in the present report are applied, however, it is no longer necessary to suppose that mechanical injury or specific arterial poisons are primarily concerned in the pathogenesis of atherosclerosis. Atherosclerosis can be considered to result as a variation of a physiologic mechanism rather than as a purely pathologic process in which peculiar materials are introduced into the arterial wall. The localized character of intimal plaques can be attributed to secondary rearrangement of lipid within the intima and the uneven involvement of various arteries to unequal arterial pressures in upright, biped man.

Anitschkow's original basic concept that there is a constant and continuous passage of fluid from the blood into the arterial intima is thus supported and can be enlarged on in the following manner. Atheromatous deposits may occur as a result of (a) alterations in composition of the transintimal filtrate, as in diabetes with hyperlipemia, (b) increase in total amount of fluid filtered, as in hypertension, and (c) interference

16 Anitschkow, N. Experimental Arteriosclerosis in Animals, in Cowdry, E. V. Arteriosclerosis. A Survey of the Problem, New York, The Macmillan Company, 1933, chap. 10, p. 298.

17 Hueper, W. C. Arteriosclerosis, Arch. Path. **38** 162-181 (Sept.), 245-285 (Oct.), 350-364 (Nov.) 1944, **39** 5-65 (Jan.), 171-131 (Feb.), 187-216 (March) 1945.

with the disposal or absorption of filtered substances, as in the fibrous, inelastic arteries of old age. Any one of these three abnormalities can occur without the development of significant atherosclerosis. Therefore it is likely that the disturbance of transintimal filtration must involve more than one of the three mechanisms listed before permanent deposits of lipid with the secondary reactions that characterize well formed intimal plaques can occur.

SUMMARY AND CONCLUSION

Evidence has been presented that the relative frequency with which intimal plaques are found in any one artery is not haphazard but that it is influenced in large measure by the level of arterial blood pressure in that artery in upright, sitting or standing positions. In these positions the major arteries are vertically disposed and the force of gravity is a factor in the blood pressure within them. On changing from recumbent to upright positions, the blood pressure rises at the lower end of these vertical arterial tubes and falls at the upper end.

The cerebral arterial blood pressure is less in the upright position than in the recumbent position. The fall in intracranial cerebrospinal fluid pressure on changing to an upright position from a horizontal one usually exceeds the fall in cerebral arterial blood pressure. The *relative* cerebral arterial blood pressure as compared with extra-arterial intracranial pressure is usually increased in upright positions.

In general, intimal plaques are common in arteries in which blood pressure is actually or relatively high in upright positions. Individual variations are due in part to local factors as perhaps in the coronary arteries but also to variations in body configuration that influence the levels of blood pressure in upright positions.

The head and neck and extremities in comparison with the trunk are usually shorter in women than in men. Therefore women as compared with men probably have relatively low blood pressures in arteries of the extremities but a relatively high cerebral arterial pressure in upright positions. On the other hand, the intracranial pressure of cerebrospinal fluid should be relatively lower in women than in men in these positions. The sex differences in distribution of atherosclerotic lesions can be explained by these sex differences in blood and cerebrospinal fluid pressures. Cerebral atherosclerosis and cerebral hemorrhage or infarction are more common in women than in men. Atherosclerosis of the arteries of the legs and gangrene of the foot are less common in women.

A more direct relationship between body configuration and cerebral atherosclerosis, independent of sex, was demonstrated in a group of 145 persons at necropsy. In this group cerebral atherosclerosis was as extensive or more extensive than coronary atherosclerosis in 2 of every 3

persons with a short head and neck and long spinal column. On the other hand, in 6 of every 7 persons with long head and neck measurements but short spinal columns the cerebral atherosclerosis was less extensive than the coronary atherosclerosis.

From all these observations, it is suggested that the role of arterial blood pressure in atherosclerosis is to provide the driving force that causes materials to enter the arterial intima from the blood from which atheromatous deposits are subsequently derived.

Miss Dorothy Wilens prepared the figures used in the text.

8a Loman, J , Dameshek, W , Myerson, A , and Goldman, D Effect of Alteration in Posture on Intra-Arterial Blood Pressure in Man II Pressure in the Carotid Artery in Arteriosclerosis, During Syncope and After the Use of Vasodilator Drugs, *Arch Neurol & Psychiat* **35** 1225-1232 (June) 1936

SYNDROME OF SHORT P-R INTERVAL WITH ABNORMAL QRS COMPLEXES AND PAROXYSMAL TACHYCARDIA

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In 1930 Wolff, Parkinson and White¹ described for the first time a syndrome characterized by an abnormal and distinctive type of electrocardiogram presented by healthy young people prone to paroxysmal tachycardia. Since then, more than two hundred articles on this syndrome have appeared in the literature. Most of these are reports of 1 or several cases, or deal with the mechanism of the abnormal electrocardiogram² or with that of paroxysmal tachycardia,³ based on electrocardiographic analysis,^{3b} the action of drugs,⁴ animal experimental in-

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1 Wolff, L, Parkinson, J, and White, P D Bundle Branch Block with Short P-R Interval in Healthy Young People Prone to Paroxysmal Tachycardia, *Am Heart J* 5 685, 1930

2 (a) Holtzmann, M, and Scherf, D Ueber Elektrokardiogramme mit verkürzter Vorhof-Kammer-Distanz und positiven P-Zacken, *Ztschr f klin Med* 121 404, 1932 (b) Wolfert, C C, and Wood, F C The Mechanism of Production of Short P-R Intervals and Prolonged QRS Complexes in Patients with Presumably Undamaged Hearts Hypothesis of an Accessory Pathway of Auriculo-Ventricular Conduction (Bundle of Kent), *Am Heart J* 8 297, 1933 (c) Scherf, D, and Schonbrunner, E Beiträge zum Problem der verkürzten Vorhof-Kammer-Leitung, *Ztschr f klin Med* 128 750, 1935

3 (a) Hunter, A, Papp, C, and Parkinson, J The Syndrome of Short P-R Interval, Apparent Bundle Branch Block, and Associated Paroxysmal Tachycardia, *Brit Heart J* 2 107, 1940 (b) Rosenbaum, F F, Hecht, H H, Wilson, F M, and Johnston, F D The Potential Variations of the Thorax and the Esophagus in Anomalous Atrioventricular Excitation (Wolff-Parkinson-White Syndrome), *Am Heart J* 29 281, 1945

4 Wolff, Parkinson and White¹ Scherf and Schonbrunner^{2c} Rosenbaum, Hecht, Wilson and Johnston^{3b} Roberts, C H, and Abramson, D L Ventricular Complexes of the Bundle Branch Block Type Associated with Short P-R Intervals *Ann Int Med* 9 983, 1936

vestigation⁵ and histologic study in animals and man⁶ Two extensive reviews of the literature have been published⁷ There has, however, been little of a follow-up nature In addition to the 11 cases reported in our original communication,¹ we have seen 41 new cases, making a total of 52

CLINICAL DATA

The clinical and electrocardiographic data of the new series are presented in table 1 There were 28 men (70 per cent) and 13 women in the new series, and 36 men (69 per cent) and 16 women in the two series combined When first seen, 14 of the new patients were 29 years of age or younger, and 25 were 30 years of age or older, the ages of 2 patients were not known If the age of onset of paroxysmal tachycardia in the patients with a history of paroxysmal rapid heart action is substituted for the age at which they were first seen, 21 patients were 29 years of age or younger and 18 were 30 years of age or older In the original series, 7 of the 11 patients were 29 years of age or younger when first seen, and if the age of onset of paroxysmal tachycardia is substituted for the age when they were first seen, 10 of the 11 patients were in the younger age group If the two series are combined and the age of onset of paroxysmal tachycardia is used, 31 of 50 patients were in the younger age group (29 years of age or under, 18 of whom were 19 years of age or younger) and 19 were in the older group

Eight patients in the new series had some abnormality of the heart other than the abnormal electrocardiogram or paroxysmal tachycardia, and 2 of the 11 patients in the original series had heart disease The common types of heart disease were present, except for 1 patient with a questionable vascular anomaly, none of the patients had congenital heart disease or other congenital anomalies

Paroxysmal tachycardia occurred in 25 cases (possibly 26) of the new series, and in 10 of the original 11 cases, making a total of 35 (or

5 Butterworth, J S The Experimental Production of the Syndrome of Apparent Bundle Branch Block with Short P-R Interval, *J Clin Investigation* **20** 458, 1941 Butterworth, J S, and Poindexter, C A Short P-R Interval Associated with a Prolonged QRS Complex, *Arch Int Med* **69** 437 (March) 1942

6 (a) Glomset, D J, and Glomset, A T A Morphologic Study of the Cardiac Conduction System in Ungulates, Dog, and Man I The Sinoatrial Node, *Am Heart J* **20** 389, 1940 (b) Wood, F C, Wolferth, C C, and Geckeler, G D Histologic Demonstration of Accessory Muscular Connections Between Auricle and Ventricle in a Case of Short P-R Interval and Prolonged QRS Complex, *ibid* **25** 454, 1943 (c) Ohnell, R F Pre-Excitation A Cardiac Abnormality, Stockholm, P A Norstedt och Soner, 1944

7 Ohnell^{6c} Vega Diaz, F Síndromes clinicoelectrocardiográficos de W P W (Wolff-Parkinson-White), contribución al conocimiento de su fisiopatología con presentación de cuatro casos, *Rev clin españ* **13** 287, 1944

TABLE 1—*Clinical and Electrocardiographic Data in 41 New Cases**

Case No	Age	Sex	Heart Disease	PRHA ‡	Abnormal Complexes				Normal Complexes				
					A-Vs	P-R Interval	QRS Interval	P-J Interval	A-Vs	P-R Interval	QRS Interval	P-J Interval	
1	20	M		?	L	0 08	0 12	0 20	N	0 10	0 10	0 20	Lead I
2	42	M	—	—	L	0 126	0 124	0 250	N	0 193	0 065	0 258	Lead III
3	28	M	+	+	L	0 10	0 12	0 22					
4	63	M	—	+	N	0 08	0 18	0 26					
5	27	M	+	+	N	0 08	0 17	0 25	N	0 20	0 05	0 25	
6	57	F	—	+	N	0 10	0 16	0 26	N				PRHA
7	17	M	—	—	N	0 10	0 16	0 27	N	0 18	0 08	0 26	
8	54	M	+	—	R	0 11	0 12	0 23					
9	19	M	—	+	N	0 084	0 143	0 227	N	0 171	0 082	0 253	
10	76	F	—	+	N	0 10	0 12	0 22	L				PRHA
11	45	F	—	+	N	0 08	0 12	0 20	L				PRHA
12	30	M	—	+	N	0 08	0 14	0 22					
13	?	M	?	+	R	0 07	0 15	0 22					
14	?	F	?	+	N	0 10	0 15	0 26	N				PRHA (lead I)
15	23	F	?	+	N	0 09	0 11	0 20	N	0 12	0 08	0 20	
16	44	F	+	—	R	0 10	0 17	0 27	L	0 19	0 07	0 26	
17	50	F	—	+	L	0 09	0 12	0 21					
18	68	M	—	—	L	0 11	0 14	0 25					
19	53	M	—	—	L	0 09	0 11	0 20					
20	29	M	—	—	L	0 096	0 116	0 212	N	0 153	0 068	0 221	
21	38	M	—	+	R	0 10	0 12	0 22					
22	20	M	—	—	L	0 10	0 12	0 22					
23	42	M	—	—	N	0 10	0 15	0 25	N	0 18	0 08	0 26	
24	32	M	—	+	R	0 11	0 11	0 22					
25	51	M	—	+	R	0 10	0 12	0 22					
26	22	M	—	—	L	0 08	0 14	0 22	N	0 19	0 09	0 28	
27	40	F	—	+	L	0 145	0 142	0 287	L	0 212	0 070	0 282	
28	29	M	—	+	L	0 10	0 14	0 24	N				A-V nodal beats
29	54	F	+	?	L	0 10	0 11	0 21					
30	45	F	—	+	L	0 10	0 13	0 23					
31	31	M	—	+	N	0 09	0 11	0 20					
32	22	F	—	+	N	0 08	0 12	0 20					
33	31	M	—	+	R	0 09	0 16	0 25	N				PRHA
34	13	F	—	—	L	0 10	0 14	0 24	N	0 12	0 10	0 22	
35	23	M	—	+	N	0 08	0 14	0 22					

Case No	Age	Sex	Heart Disease	PRHA ¹	Abnormal Complexes				Normal Complexes				
					Avis	P-R Interval	QRS Interval	P-J Interval	Avis	P-R Interval	QRS Interval	P-J Interval	
36	65	M	+	—	L	0 079	0 161	0 240	L	0 145	0 111	0 256	After digitalis
37	47	M	+	+	L	0 12	0 14	0 26					
38	44	M	—	—	L	0 10	0 16	0 26					
39	22	M	—	—	L	0 094	0 188	0 282	N	0 194	0 103	0 297	
40	41	M	+	+	L	0 12	0 12	0 26	N				PRHA
41	47	F	'	+	L	0 09	0 14	0 23					

*In this table, the minus sign indicates absence of, and the plus sign presence of, heart disease, the question mark, unknown, L indicates left axis deviation, R, right axis deviation, N, normal axis, PRHA, paroxysmal rapid heart action, and P-J interval, sum of P-R interval and QRS intervals. All measurements were made with a hand lens, those given to the third decimal place were made with a Lucas comparator. Measurements in this, and in all other tables, are expressed in seconds.

36) cases with paroxysmal tachycardia in the combined series of 52 cases. The clinical features were similar to those in ordinary cases of paroxysmal tachycardia. The attacks occurred as often as from twelve times a day to once or twice a year and lasted from several minutes to ten days. Precipitating factors were effort, fatigue, stress, trauma, anger, laughing or other expressions of emotion, expectorating, excessive drinking and pneumonia, or the cause was unknown. The attacks ended spontaneously, or as a result of holding the breath, placing the head between the knees, lying down, vomiting, stimulation of the carotid sinus or administration of digitalis, quinidine or ipecac. In 1 case methacholine chloride (mecholy chloride^R) failed to stop an attack, as did vomiting and stimulation of the carotid sinus in another. As might be expected in patients with normal hearts, the symptoms during paroxysms were palpitation, painful palpitation, apprehension, giddiness, fatigue, weakness, faintness, loss of consciousness, sweating, precordial pain and a sense of suffocation.

Five of the 41 new patients had disease of the thyroid gland, including 1 with acute thyroiditis and another with thyrotoxicosis. One patient had Raynaud's disease, scleroderma, gangrene of the toes and gallstones, 1, dementia paralytica, 1, fever of unknown origin, 1, probable rheumatic fever, and another, active pulmonary tuberculosis. One patient was seen during pregnancy, which ran a normal course and ended in a normal, uneventful delivery. Another patient with pneumonia and treated syphilis was an addict to morphine and alcohol. Three patients came to our attention for evaluation as surgical risks prior to operation for, respectively, uterine fibroids and endometrial polyps, benign prostatic

hypertrophy and cataract. Surgical treatment in each instance was uneventful, as was subtotal thyroidectomy for thyrotoxicosis in another patient. One patient had diverticula of the sigmoid and duodenal ulcer, and 1 patient was mentally defective.

Except for the various diseases noted, the general health of the patients was good. Symptoms from paroxysmal tachycardia usually were not severe, but resulted in chronic invalidism and incapacity in several cases. In still others ill health resulted from a wrong diagnosis of heart disease or an incorrect interpretation of the electrocardiogram.

A mistaken diagnosis of heart disease, often one of serious heart disease, was made in 15, or more than one third, of the cases. In 12 cases the error, at least in part, was based on an incorrect interpretation of the electrocardiogram. Misinterpretation of benign murmurs, reduplication of the first apical heart sound, which is frequently present in these cases, and failure to recognize paroxysmal tachycardia as being the cause of symptoms also played a part in the wrong diagnosis of heart disease. Some of the mistaken diagnoses were myocarditis, disease of the coronary arteries, defect of the interventricular septum, congenital heart disease, mitral stenosis, acute coronary thrombosis, neurocirculatory asthenia, nocturnal paroxysmal dyspnea and congestive heart failure. The commonest mistaken electrocardiographic interpretations were left bundle branch block and paroxysmal ventricular tachycardia.

CLINICAL COURSE

The life history of the patients under discussion is not different from that of other persons with normal hearts or of those subject to paroxysmal tachycardia whose electrocardiograms are normal. Except for limitations imposed by paroxysmal tachycardia in some of them, they live normal, unrestricted lives. Many of our patients were healthy, vigorous athletes, accustomed to strenuous activity, some were exposed to the hardships of military life, without unusual strain. Intercurrent disease, severe infections, such as pneumonia and septicemia, major surgical procedures, and pregnancy were borne in the same manner as by other patients. The same was true of ordinary antisyphilitic treatment and malarial therapy. In none of our patients did subacute bacterial endocarditis develop. The clinical course of those who coincidentally acquired heart disease does not appear to be altered by the abnormal electrocardiogram or by an unusual propensity to paroxysmal tachycardia. Patient 40, who had severe rheumatic heart disease and intractable congestive failure, died of ventricular fibrillation, and patient 37, with hypertensive heart disease, died with uremia. There is no evidence that patients in this group are more prone than others to have heart disease, although congestive failure rarely may result from uncontrolled tachy-

cardia, as noted later. No patient in this series died as a consequence of the abnormal cardiac mechanism.

Paroxysmal tachycardia began at the age of 47 in patient 4, who has been under observation from the age of 63 to that of 72 (at the time of writing), his heart is normal and he is in good health. Patient 10, with a history of paroxysmal tachycardia, had a normal heart and was in good health at the age of 76. In spite of mitral stenosis, and the presence of paroxysmal tachycardia since early childhood, patient 3 was in good health, except for symptoms due to paroxysmal tachycardia, when seen at the age of 28. Fever of unknown origin was present during the eight years that patient 8 was under observation, but there were no cardiac symptoms or signs of heart disease except for the abnormal electrocardiogram. Patient 23 was under observation from the age of 42 to that of 51 years, he never had paroxysmal tachycardia, and his heart was normal. Patients 12 and 33 had normal hearts at 30 and 31 years of age, respectively, and had had paroxysmal tachycardia for ten and eleven years. Patient 31 had a normal heart at the age of 31 and had had paroxysmal tachycardia for at least twenty years. Patient 28, at the age of 40, had a normal heart and had had paroxysmal tachycardia for eight years. With a history of paroxysmal tachycardia as long as she could remember, patient 30, at 45 years of age, had a normal heart, patients 11 and 21 had normal hearts at 45 and 38 years of age, respectively, and had had paroxysmal tachycardia for twenty-eight and twenty-four years, respectively.

CASE 1 (original series¹) —This case is of historical interest, being the first in which the combination of short P-R interval, abnormal QRS complexes and paroxysmal tachycardia was recognized as a distinct clinical entity. The patient was 35 years old when we first saw him, in 1928. He gave a history of paroxysmal auricular tachycardia and paroxysmal auricular fibrillation for ten years, but his occupation was that of a physical director, and he engaged in strenuous athletic activity without difficulty. In 1935, after he had had untreated persistent auricular fibrillation for six months, he was examined at another clinic,⁸ where congestive failure and moderate cardiac enlargement were found. Digitalization and administration of quinidine restored normal rhythm. Improvement was striking, and, in spite of an occasional paroxysm of auricular fibrillation, he was able to carry on well. In 1939 the transverse diameter of the heart was 14.8 cm, as compared with 14.1 cm in 1928. He was last examined in January 1947, at the age of 54, nineteen years after our first examination and twenty-nine years after the onset of paroxysmal tachycardia. He was in good health except for rare paroxysms of tachycardia (none for over a year). He was taking 1 tablet of quinidine every morning. He was less strenuous than he used to be but was still doing gymnasium work and acting as a referee. The pulse was regular, at 82 per minute, the blood pressure was 130 systolic and 90 diastolic, the heart sounds were good,

8 (a) Levine, S. A., and Beeson, B. The Wolff-Parkinson-White Syndrome, with Paroxysms of Ventricular Tachycardia, *Am Heart J* 22: 401, 1941. (b) Wolff, L. Familial Auricular Fibrillation, *New England J Med* 229: 396, 1943.

and there were no murmurs. An electrocardiogram showed a full P-R interval and normal ventricular complexes. With fluoroscopic examination, the size and shape of the heart appeared normal, as did the aorta. An orthodiagram showed that the transverse diameter of the heart measured 12.0 cm and the internal diameter of the thorax 28.0 cm. There was no evidence of heart disease.

CASE 2 (first series¹) —The patient was first seen in March 1928, when he was 18½ years old. He had had paroxysmal tachycardia four years. He was a robust athlete, apparently in excellent health. In 1936 he reported that he had had no paroxysmal tachycardia for three years, while in medical school. One paroxysm occurred in January 1937, when he was tired, at the end of a strenuous internship. His heart appeared normal on examination, and in the orthodiagram the transverse diameter of the heart was 12.3 cm and the internal diameter of the chest 28.3 cm.

He was last seen on Jan. 9, 1946, after having served forty months in the Army, twenty-seven of them in the European and North African theaters. This was eighteen years after our first examination. Only two paroxysms of tachycardia had occurred in the past six years, one at rest and one after a blow on the chest. He was 36 years old, and he had had paroxysmal tachycardia for twenty-two years. The heart was normal on examination, the electrocardiogram showed a short P-R interval and anomalous QRS complexes, and the total transverse diameter of the heart was 12.9 cm as seen in the orthodiagram.

CASE 49 (first series¹) —The patient was 16 years old when first seen in 1926. He complained of attacks of sudden tachycardia, generally on exertion, there was no history of rheumatic fever or evidence of heart disease. In 1933 he was in good health, except for an occasional brief attack of palpitation, and the electrocardiogram was normal. He was at work and in good health in 1938, and the electrocardiogram showed normal complexes in lead I and short P-R intervals and widened QRS complexes in leads II and III, resembling exactly the electrocardiograms taken in 1926 (figs. 9, 10 and 11 in our first paper¹). Pulmonary tuberculosis developed in 1947, and the patient was invalided from the Navy. In February 1948, twenty-two years after he was first seen, he wrote that he had had six attacks of palpitation (rate, 240 a minute) during four months in bed, the longest attack lasting six hours. His symptoms otherwise were those of the pulmonary infection.

CASE 7 (first series¹) —The patient was first seen in 1929, when he was 11 years old. At 17 years of age he was playing all games and was well except for occasional attacks of migraine, the electrocardiogram was abnormal and similar to the one recorded in 1929 (fig. 15¹). He joined the Army in 1940 and served abroad until June 1946. He was not subject to paroxysmal tachycardia but had occasional attacks of faintness, during which the pulse rate fell to 30 to 40 per minute. He never lost consciousness, however, and recovery was so rapid that these attacks did not interfere with his war service. In February 1948, at the age of 30, and nineteen years after the abnormal electrocardiogram was first recorded, he reported for examination on request and said he was well. The blood pressure was 140 systolic and 80 diastolic, and roentgenoscopic examination showed a heart of normal shape and size. The electrocardiogram was abnormal and almost identical with the original record (fig. 15¹).

9 Sir John Parkinson, London, furnished the follow-up notes on this case (patient 4) and on the next 2 cases.

CASE 8 (first series¹) —The patient was first seen in 1925, when she was 16 years old. There was a history of alleged heart trouble. She had been quite well until two years before, when she began to be breathless at dancing and hockey. One night she felt a throbbing in her neck, which kept her awake. She was examined again in 1929. She was a university student and was active and well, her only complaint being that of easy fatigue. This patient was traced and came for reexamination on Jan. 29, 1948, twenty-three years after our first examination. She was 39 years of age, married, and had a son aged 12. She was well and had no complaints. Examination revealed nothing abnormal. The blood pressure was 115 systolic and 75 diastolic, and roentgenologic examination showed a heart of

TABLE 2—*Measurements in Seconds, Made with a Lucas Comparator in 5 Electrocardiograms Displaying Both Normal and Abnormal Complexes**

Case No †	P-R Interval	QRS Interval	P-J Interval	P-R Difference	P-J Difference
2					
A	0 126	0 124	0 250	—0 067	—0 008
N	0 193	0 065	0 258		
9					
A	0 084	0 143	0 227	—0 087	—0 026
N	0 171	0 082	0 253		
20					
A	0 096	0 116	0 212	—0 057	—0 009
N	0 153	0 068	0 221		
27					
A	0 145	0 142	0 287	—0 067	+0 005
N	0 212	0 070	0 282		
39					
A	0 094	0 188	0 282	—0 100	—0 015
N	0 194	0 103	0 297		

*Lead III was used in case 2, lead II in the others.

†A indicates abnormal complexes, N, normal complexes.

TABLE 3—*Effect of Digitalis on the Various Intervals, Measured in Seconds with Lucas Comparator*

Case No	Digitalis U S P, Gm	P-R Interval	QRS Interval	P-J Interval	P-R Peak Interval	QRS Difference
2	0	0 116	0 150	0 266	0 220	
	2 2	0 114	0 172	0 286	0 198	+0 022
36	0	0 079	0 161	0 240	0 172	
	2 1	0 080	0 159	0 239	0 166	—0 002

normal size and contour. The electrocardiogram showed normal P-R intervals and normal ventricular complexes and was identical with one taken nineteen years previously (fig. 17¹).

ELECTROCARDIOGRAPHIC DATA

All the patients, of course, at some time had electrocardiograms which displayed short P-R intervals and anomalous ventricular complexes, and at such times the heart rate usually was slow and sinus arrhythmia often was present. Over a period of years in a given case, only

one electrocardiogram, or an occasional one of many taken, may show the abnormal type of curve. In 1 case the first electrocardiogram was abnormal, and twelve subsequent ones, taken over many years, were normal. In another case the abnormal type of electrocardiogram was first recorded several years after the first observation, although there was no

TABLE 4—*Circumstances in Which Normal Complexes Occurred in 21 Cases and Number of Cases in Which an Attempt Was Made to Alter the Abnormal Electrocardiogram**

Case No	Spon- taneous Appear- ance	Paroxysmal Rapid Heart Action	Exercise	Atropine	Quinidine	Valsalva Experiment
1				+		
2	+		—	—		
4			—			
5	+	+				
6		+				
7	+					
9	+					
10		+				
11		+				
12		—	—	—		
13		—		—		
14		+				
15	+	+				
16	+					
18				—		
20	+		—	—		
22			—			
23	+		—			
24			—	—		
25			—	—		
26	+					
27	+					
28			A-V nodal		A-V nodal	A-V nodal
30				—		
33		+	+			
34				+		
36	+					
39	+					
40		+			+	

*The + sign indicates appearance of normal complexes — persistence of abnormal complexes during paroxysmal rapid heart action or with the various procedures used, and A-V nodal appearance of normal complexes with auriculoventricular nodal beats

change in the clinical picture and no reason to suspect the intercurrent development of heart disease or any change in the cardiovascular system. The instantaneous electrical axis was normal in 14 cases and deviated to the left in 20 cases and to the right in 7 cases. When normal ventricular complexes were present (21 cases), the axis was normal in 16 and deviated to the left in 5 (table 1). The P-R interval, which varies within wide limits in the various limb, precordial and esophageal leads, was measured in lead II in all but 3 of our cases, it was 0.10 second or less in 34 cases, 0.11 second in 3 cases, 0.12 second in 3 cases and 0.14 second in 1 case. The anomalous ventricular complexes in lead II measured 0.11 to 0.12 second in 17 cases, 0.13 to 0.14 second in 12

TABLE 5—*P-J Intervals in 41 Cases of Anomalous Conduction, 97 Cases of Right Bundle Branch Block and 15 Cases of Left Bundle Block*

P-J Interval, Sec	Anomalous Conduction	RBBB*	LBBB*
0.20	6	0	0
0.21	3	0	0
0.22	11	0	0
0.23	3	3	0
0.24	3	3	0
0.25	5	9	0
0.26	6	12	1
0.27	2	14	0
0.28	1	8	1
0.29	1	5	1
0.30+	0	43	12

*In this table, RBBB indicates right bundle branch block, and LBBB, left bundle branch block.

cases, 0.15 to 0.16 second in 8 cases and 0.17 to 0.20 second in 4 cases. The P-J interval (sum of the P-R and QRS intervals) was 0.20 to 0.26 second in 37 cases and 0.27 to 0.29 second in 4 cases (table 5). The electrocardiogram in 5 cases displayed both normal and abnormal complexes, and measurement of the various intervals, made with a Lucas comparator, are shown in table 2.

In 21 of the 41 cases electrocardiograms displayed normal ventricular complexes under various conditions (table 4), of the other 20 cases, only one electrocardiogram was taken in 11 and only two in 6. In 12 cases normal ventricular complexes occurred spontaneously—in 2, after the administration of atropine, in 6, during paroxysmal auricular tachycardia, and in 3, during paroxysmal auricular fibrillation, in 1 case the only normal ventricular complexes were A-V nodal premature beats, which occurred with exercise, during a Valsalva experiment and after

the administration of quinidine. An attempt was made to alter the abnormal electrocardiogram in 16 cases. Exercise and atropine, each used in 10 cases, were effective in doing so in 1 and 2 cases, respectively, quinidine was effective in 1 of 2 cases, and the Valsalva experiment, in the 1 case in which it was tried (table 4)

Digitalis was used experimentally in 1 case and therapeutically in another. The measurements of the various intervals, before and after digitalization, made with a Lucas comparator, are shown in table 3. In case 2 the "anomalous component" of the QRS group began in the same manner before and after the oral administration of 2.2 Gm of digitalis U S P in eighty-four hours, but the sharp upstroke (lead II) following

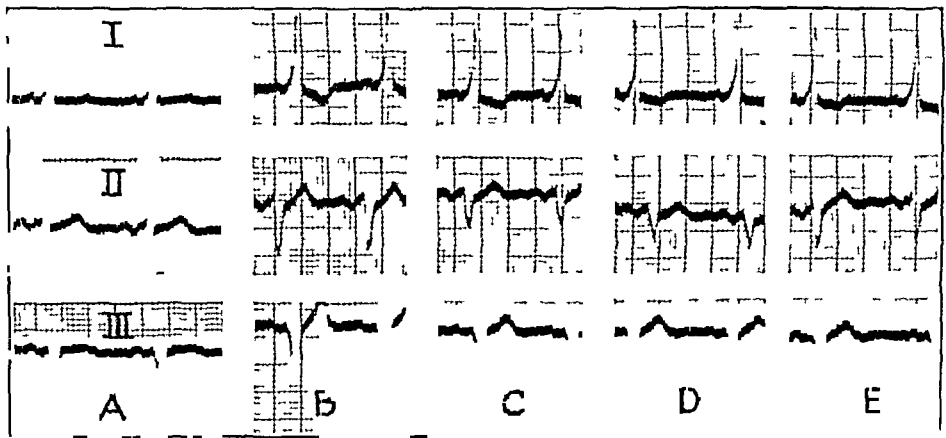


Fig. 1 (case 2)—Effect of digitalis on the abnormal electrocardiogram (table 3). *A* is a control record, before administration of digitalis, *B* was taken after administration of digitalis, *C*, one-half hour after the subcutaneous injection of 1.2 mg of atropine, *D*, one hour after administration of atropine, *E*, one and one-half hours after administration of atropine.

the "anomalous component" was missing after digitalis, these changes were not abolished with atropine (fig. 1). In case 36, after the oral administration of 2.1 Gm of digitalis U S P in seven days, the rate dropped from 95 to 45, and a sharp upstroke, previously not present, followed the premature component (lead II), the steplike appearance of the latter was not apparent after administration of digitalis (fig. 2).

PAROXYSMAL TACHYCARDIA

A record of paroxysmal rapid heart action was obtained in 10 cases of the new series and in 3 cases of the old series. Paroxysmal auricular tachycardia was present in 8 cases, paroxysmal auricular flutter in 2 cases and paroxysmal auricular fibrillation in 3 cases. The ventricular rate was 190 to 260 in 11 cases, 150 in 1 case and 156 in 1 case. In all but 2 of the 13 cases normal ventricular complexes were present during the tachycardia. Of these 2 cases, electrocardiograms (mostly during nor-

mal rhythm) were obtained twenty times in one and on eighteen occasions in the other, and in none of these electrocardiograms were normal ventricular complexes seen, in 1 of these cases exercise and atropine failed to alter the abnormal electrocardiogram. In 3 cases, during paroxysmal auricular fibrillation, normal ventricular complexes were temporarily interrupted by short runs of anomalous ventricular complexes, usually at a very rapid rate, similar to those seen with normal sinus rhythm (fig 3). Twenty electrocardiograms were obtained in case 12, including those after exercise and atropine, none of them showed normal ventricular complexes. With tachycardia, at a rate of 220, the ventricular complexes were abnormal and similar to those during normal sinus rhythm except for minor differences (fig 4). Small deflections of the P waves are seen in the standard limb leads. Eighteen electrocardiograms were obtained in case 13, and none of them showed normal ventricular

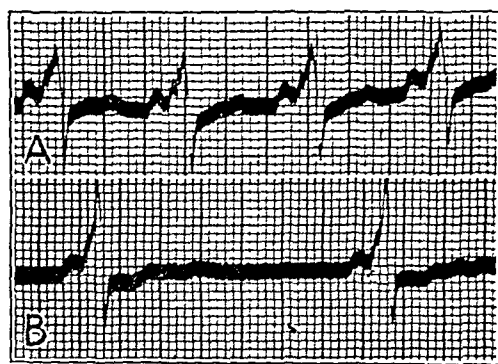


Fig 2 (case 36) —Effect of digitalis on the abnormal electrocardiogram (table 3). *A* is lead II before administration of digitalis, *B*, lead II after administration of digitalis.

complexes. One record was obtained during tachycardia due to auricular flutter, the ventricular complexes were abnormal, but unlike those obtained with normal rates (fig 5).

COMMENT

It has been suggested that the syndrome under discussion is seen most commonly in older age groups,¹⁰ and that it may be acquired as the result of heart disease.⁷ While the latter possibility cannot be denied, there is no proof that it ever happens. Since its recognition depends on the finding and proper interpretation of the characteristic electrocardiogram, it is obvious that the condition may be present for many years without detection, either because electrocardiograms were not obtained, or because the anomalous pathway was not functioning when electrocar-

¹⁰ Willius, F. A., and Carryer, H. M. Cardiac Clinics. Electrocardiograms Displaying Short P-R Intervals with Prolonged QRS Complexes, an Analysis of Sixty-Five Cases, Proc. Staff Meet., Mayo Clin. 21: 438, 1946.

diagrams were recorded. This factor has a bearing also on the incidence of the syndrome. While it is our belief that the syndrome is a common disorder, its exact incidence would be known only if it were possible regularly to induce the anomalous pathway to function, as it is now possible in some cases to suppress the abnormal mechanism. That the disorder occurs in young children and during adolescence is evident from our own experience and that of many other authors. It is also clear that the disorder will be recognized oftenest in those age groups in which electrocardiograms are most frequently taken, the older age groups, but this

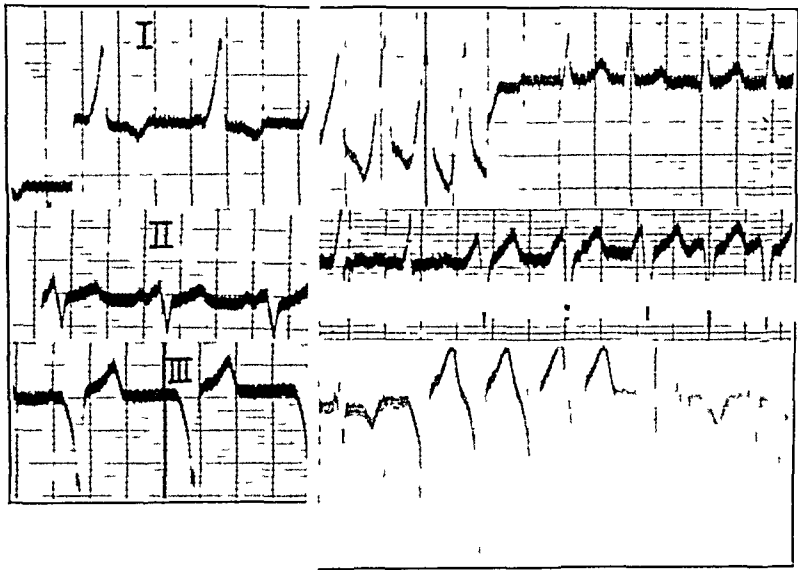


Fig 3—Abnormal QRS complexes with normal rhythm (left hand tracings) and with paroxysmal auricular fibrillation (right hand tracings). See text.

does not mean it is commonest in such patients. Paroxysmal tachycardia is a characteristic feature of the disorder and may be its first manifestation, the age of its onset clearly indicates that the abnormal mechanism is present in early life in the majority of the patients. Additional information concerning age incidence should be obtained by routine and special electrocardiographic study in children.

It is interesting that a mistaken diagnosis of heart disease was made in more than one third of the cases, largely as the result of incorrect interpretation of the electrocardiogram. It may be profitable, therefore, to discuss the diagnostic features of the electrocardiogram, as well as methods of avoiding misinterpretation. The wide QRS waves suggest bundle branch block, but as a rule, instead of distinct notching, a heavily slurred deflection of small amplitude, the so-called anomalous component, initiates the QRS group. This "anomalous component" may be more striking in unipolar precordial leads than in the standard limb leads. Of greater importance is the absence, in unipolar precordial leads, of

the features which are diagnostic of bundle branch block¹¹ The P-R interval in most of the cases was 0.10 second or less and in only 1 case was greater than 0.12 second This interval should be measured in all leads, as the "anomalous component" may be difficult to recognize in a given lead, with the result that measurement of the P-R and QRS intervals (figs 4 and 6) are incorrect In the vast majority of cases of anomalous conduction the P-J interval is 0.26 second or less, and is usually greater than this value in cases of bundle branch block (table 5) If many electrocardiograms are taken, there is a greater probability of recording normal, as well as abnormal, ventricular complexes, and if the P-J intervals of the normal and the abnormal ventricular complexes

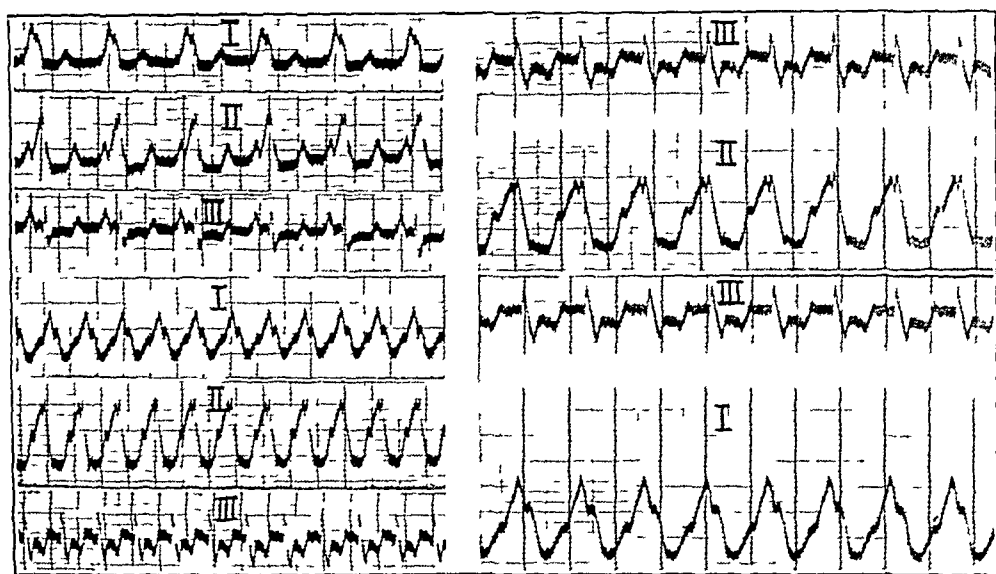


Fig 4 (case 12) —First column, from above downward leads I, II and III, during normal rhythm and leads I, II and III, during paroxysmal tachycardia Second column, from above downward first strip simultaneous leads III and II, second strip simultaneous leads III and I, paroxysmal tachycardia with film running at high speed Note similarity of QRS complexes during normal rhythm and paroxysmal tachycardia, the P deflections during paroxysmal tachycardia and the isoelectric "anomalous component" in lead III

are identical, it may be assumed that the abnormal electrocardiogram is due to the mechanism under discussion, and not to bundle branch block In doubtful cases it is helpful if the electrocardiogram can be altered by various procedures, such as exercise or use of drugs, effects of which are presented in table 6 Only those effects are listed which may help in the interpretation of a doubtful electrocardiogram, and it is not implied that these effects always occur

11 Wilson, F N, Johnston, F D, Rosenbaum, F F, Erlanger, H, Kossmann, C E, Hecht, H, Cotrim, N, de Oliveira, R M, Scarci, R, and Barker, P S The Precordial Electrocardiogram, *Am Heart J* 27 19, 1944

THE ABNORMAL CARDIAC MECHANISM

In 1928, when for the first time we saw and recognized as an entity the type of electrocardiogram under discussion, it was natural to consider the wide QRS complex as being due to bundle branch block.¹ In 1929, before the publication of our original paper,¹ we considered the possibility of premature activation of part of the ventricular muscle by

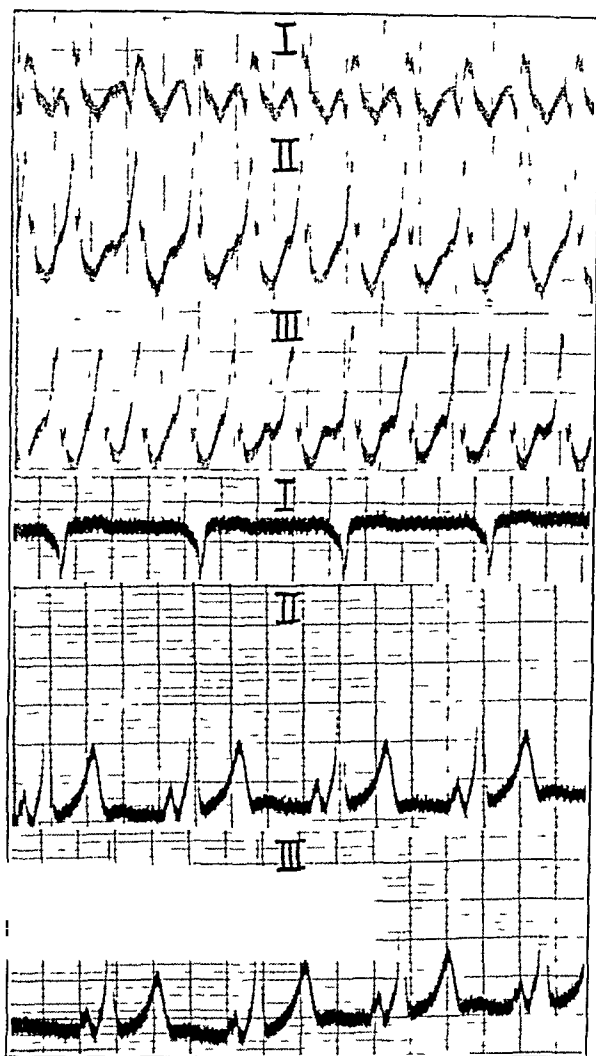


Fig 5 (case 13) —From above downward leads I, II and III, during tachycardia, and leads I, II and III, during normal rhythm. The ventricular complexes are abnormal, but dissimilar, with both rhythms. The tachycardia is due to auricular flutter, and the ventricles are responding to auricular impulses.

way of a congenital accessory conducting pathway as the cause of the short P-R interval and wide QRS waves. As a matter of fact, a paper containing a theoretic discussion of this mechanism was written but, because of its highly speculative nature, was not published. We mention

these facts, not to raise any question of priority, which properly belongs to both Holtzmann and Scherf,^{2a} and Wolferth and Wood,^{2b} but to call attention to the fact that as early as 1929 we abandoned the concept of bundle branch block. The experimental production of this type of electrocardiogram,⁵ the careful mapping of the potential variations of the

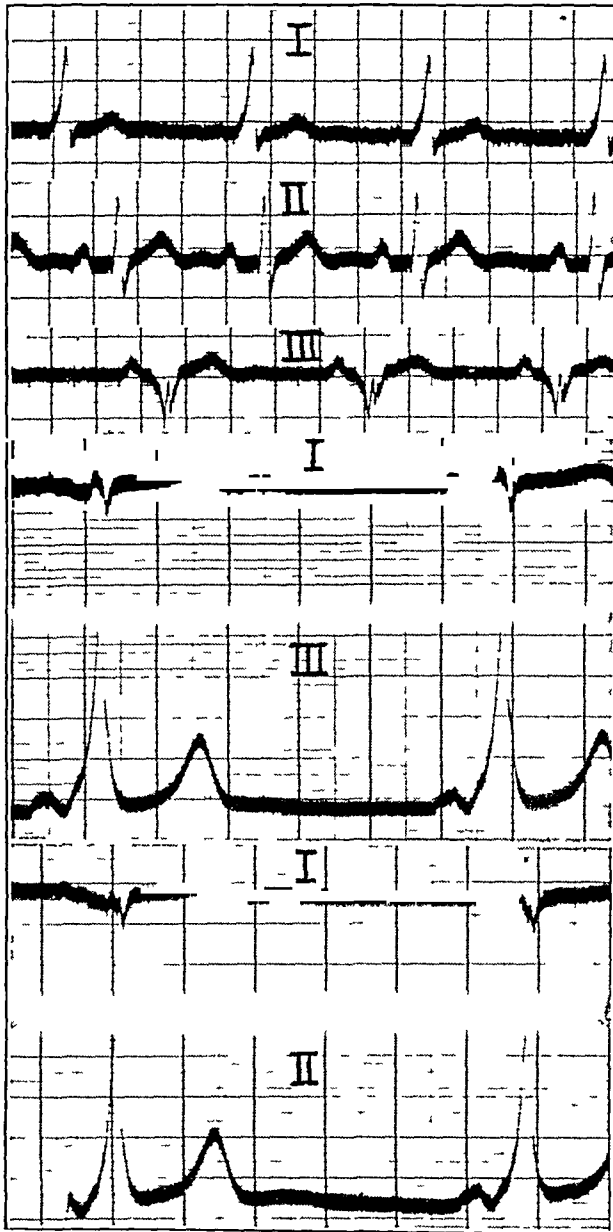


Fig 6—Upper three strips (case 1) leads I, II, and III, lower two strips (case 13) simultaneous leads I and III, and simultaneous leads I and II, from above downward. Note difficulty in recognizing the "anomalous component" in some of the leads.

thorax and esophagus^{3b} and the histologic demonstration of accessory conducting pathways in patients with this type of electrocardiogram^{6b, c} have established the presence of some sort of accessory conducting pathway as the most likely explanation of the abnormal electrocardiogram.

Although ventricular depolarization is initiated prematurely through an accessory conducting pathway, the impulse traversing the normal auriculoventricular connections ultimately arrives at ventricular muscle not yet reached by anomalous excitation, and depolarization of the entire ventricular mass is completed. Assuming this to be true, the P-R interval will be shortened to the same extent that the QRS interval is lengthened. In records showing both anomalous and normal complexes, therefore, the P-J intervals of the two types should be the same, or nearly the same, and actual measurement of these intervals has shown this to be true in

TABLE 6 —Possible Effect of Various Procedures on the Electrocardiogram of the Normal Heart and Those of "Anomalous" Conduction and Bundle Branch Block

	Effect on Normal Electrocardiogram	Effect on Anomalous Electrocardiogram of Anomalous Conduction	Effect on Electrocardiogram of Bundle Branch Block
Exercise	—†	Normal QRS	—
Carotid sinus stimulation	May produce anomalous QRS complexes‡	A-V nodal rhythm with normal QRS	—
Valsalva experiment	May produce anomalous QRS complexes‡	A-V nodal rhythm with normal QRS	—
Atropine	—	Normal QRS	—
Amyl nitrite	—	A-V nodal rhythm with normal QRS	—
Neo-Syneprine ^R (phenylephrine)	—	A-V nodal rhythm with normal QRS	—
Quinidine	Widens QRS	Normal QRS	Widens QRS
Digitals Mechoyl ^R (methacholine) Neostigmine	—	May widen, diminish or have no effect on QRS	—

*Only those effects are listed which may have a bearing on interpretation of "anomalous" electrocardiograms

†The minus sign indicates no effect

‡This effect may occur when the experiment is done during the presence of a normal electrocardiogram in cases of short P-R interval and abnormal QRS complexes

some instances, but not in all. We were able to make these measurements in 5 cases, and the P-J intervals with normal and with anomalous conduction were nearly the same in 3 cases and were different in 2, the anomalous P-J intervals being 0.026 and 0.015 second, respectively, shorter than the normal P-J intervals (table 2). A similar discrepancy was found on two occasions in a case studied by Kossmann and Goldberg,¹² the P-J interval being greater with normal than with abnormal conduction, and the difference in the P-R intervals with the two types

12 Kossmann, C. E., and Goldberg, H. H. Sequence of Ventricular Stimulation and Contraction in a Case of Anomalous Atrioventricular Excitation, *Am Heart J* 33: 308, 1947

of conduction being 0.075 and 0.080 second, respectively. These authors interpreted these values, and other data discussed by them, to mean that depolarization of the ventricles was mediated entirely through an accessory pathway and that there was no conduction through the normal auriculoventricular conducting system when the QRS complexes were anomalous. After examining the existing data, they concluded that when the P-R interval is shortened during anomalous conduction beyond a certain critical value, which they placed at 0.06 second, anomalous excitation is so premature that it has time to spread and depolarize so much of the ventricular mass that the latter is refractory when the impulse via the normal auriculoventricular connections reaches the ventricles. Although there are other possible explanations for discrepancies in the P-J interval, the evidence in their case warrants the conclusion which they reached.

The discrepancy in the P-J intervals in our cases can also be explained by depolarization of the entire ventricular mass via the anomalous route, due to critical shortening of the P-R interval, but our findings suggest that the critical value is probably nearer 0.08 second than the 0.06 second arrived at by Kossmann.

The magnitude of shortening of auriculoventricular conduction time when the anomalous pathway functions is of interest from another point of view. The form of the anomalous complex undoubtedly is determined by the place at which premature depolarization begins, by the number of such possible places and by the order of auricular excitation. It has been suggested¹³ that electrocardiograms showing a short P-R interval without abnormal widening of the QRS complex, of which 4 cases have been reported,¹⁴ may be explained by the termination of an accessory tract in the septum near the bundle of His. This tract was actually demonstrated histologically in 1 of these cases.^{6c} However, the amount of shortening of the anomalous P-R interval must also exert an influence on the QRS deflections, and it is easy to imagine a difference between normal and anomalous auriculoventricular condition intervals of such small magnitude that depolarization of most of the ventricular mass proceeds along the normal pathways. Under these conditions, it might be expected that the electrocardiogram would display short P-R intervals but little else, if the normal P-R interval then increased by small

13 Burch, G. E., and Kimball, J. L. Notes on the Similarity of QRS Complex Configurations in the Wolff-Parkinson-White Syndrome, *Am Heart J* 32: 560, 1946.

14 Ohnell.^{6c} Burch and Kimball.¹³ Fox, T. T. Aberrant Atrio-Ventricular Conduction in a Case Showing a Short P-R Interval and an Abnormal But Not Prolonged QRS Complex, *Am J M Sc* 209: 199, 1945. Littmann, D. Aberrant Auriculo-Ventricular Conduction in a Patient with Paroxysmal Tachycardia, a Short P-R Interval and a Normal QRS Complex, *Am J Med* 2: 126, 1947.

increments, a series of transitional complexes would result. If the normal P-R and QRS intervals were 0.13 and 0.07 second, respectively, these intervals would become 0.12 and 0.08 second, respectively, during anomalous conduction with an auriculoventricular interval of 0.12 second. On the other hand, it would not be possible to recognize anomalous conduction, without altering the electrocardiogram (table 6), if the anomalous P-R interval were 0.16 second and the normal P-R interval 0.17 second. This may be the reason that "delayed anomalous conduction," which would furnish the final link in the chain of evidence for a functioning structural accessory pathway, has never been observed. It may also explain the narrow range of observed anomalous P-R intervals, as compared with the wide range of the normal P-R interval. Whereas the smallest value for the anomalous P-R interval is conditioned by the fastest speed of conduction of which the tissues of the hypothetic accessory pathway are capable, considerably slower rates of conduction might result in anomalous P-R intervals so closely approximating the normal P-R interval that the anomalous character of the electrocardiogram would not exist, or would not be recognizable.

PAROXYSMAL TACHYCARDIA

With few exceptions, published electrocardiograms of paroxysmal tachycardia have shown normal ventricular complexes. Arana and Cossio¹⁵, Hunter, Papp and Parkinson^{3a}, Levine and Beeson^{8a}, Palatucci and Knighton¹⁶, Missal, Wood and Leo,¹⁷ and Klainer and Joffe¹⁸ reported a total of 9 cases and published the electrocardiograms in 7 of their cases of paroxysmal tachycardia with abnormal ventricular complexes, a condition which they interpreted as paroxysmal ventricular tachycardia. Inspection of the published electrocardiograms, however, suggests to us the possibility of supraventricular tachycardia and anomalous condition. Palatucci¹⁶ and Missal,¹⁷ while reporting their cases as instances of ventricular tachycardia, frankly admitted that auricular fibrillation and aberrant ventricular condition could not be excluded.

15 Arana, R., and Cossio, P. Fibrilación auricular y taquicardia ventricular como eventualidad posible en el P-R corto con Q-R-S ancho y mellado, *Rev argent de cardiol* 5:43, 1938.

16 Palatucci, O. A., and Knighton, J. E. Short P-R Interval Associated with Prolongation of QRS Complex. A Clinical Study Demonstrating Interesting Variations, *Ann Int Med* 21:58, 1944.

17 Missal, M. E., Wood, D. J., and Leo, S. D. Paroxysmal Ventricular Tachycardia Associated with Short P-R Intervals and Prolonged QRS Complexes, *Ann Int Med* 24:911, 1946.

18 Klainer, M. J., and Joffe, H. H. A Case of Short P-R Interval and Prolonged QRS Complex with a Paroxysm of Ventricular Tachycardia, *Ann Int Med* 24:920, 1946.

Movitt¹⁹ at first made a diagnosis of paroxysmal ventricular tachycardia in his case and later correctly changed it to auricular fibrillation and anomalous conduction. Abnormal ventricular complexes were present in 5 of the 13 records of tachycardia in our cases, in 3 of them as short runs of very rapid rate temporarily interrupting normal ventricular complexes during paroxysmal auricular fibrillation. The resemblance of the abnormal ventricular complexes during tachycardia to the anomalous complexes seen with sinus rhythm, the identification of P waves regularly related to the QRS complex in 1 of the cases of paroxysmal auricular tachycardia and the presence of auricular flutter in another case clearly indicate that the abnormal ventricular complexes were due to anomalous conduction associated with supraventricular rhythm, and not to paroxysmal ventricular tachycardia. This proves that the accessory pathway is capable of transmitting impulses at extremely rapid rates, a point of considerable interest, since, on the one hand, the heart rate has been considered by some as vital in determining whether or not anomalous conduction will occur and, on the other, the accessory pathway, by delivering impulses to the auricle, has been thought to initiate and maintain paroxysms of tachycardia. The importance of recognizing anomalous conduction associated with supraventricular rhythm, and avoiding a mistaken diagnosis of paroxysmal ventricular tachycardia, is self evident.

EFFECT OF DIGITALIS ON THE ABNORMAL MECHANISM

Scherf and Schonbrunner^{2c} observed the disappearance of the abnormal ventricular complexes following digitalization and concluded that digitalis had a greater affinity for the anomalous than for the normal auriculoventricular connections. The short P-R interval remained unchanged in our 2 cases after full digitalization, but anomalous complexes disappeared entirely later, whether as the result of digitalis or not we are unable to say. In case 40, as in Movitt's case,¹⁹ digitalis seemed ineffective in slowing the ventricular rate during auricular fibrillation when anomalous ventricular complexes were present. In case 2 the anomalous QRS interval increased 0.022 second after digitalization, but in case 36 the QRS interval remained unchanged (table 3). Unfortunately, normal complexes were not present in these electrocardiograms, but it is probable that the normal P-R interval increased in both cases after digitalization, especially in case 36, in which the heart rate decreased from 95 to 45. There can be little doubt that the increase of the QRS interval in case 2 is due to lengthening of the normal P-R interval, but the increment in these measurements is not necessarily the same, as

¹⁹ Movitt, E. R. Some Observations on the Syndrome of Short P-R Interval with Long QRS, *Am Heart J* 29:78, 1945.

implied by Fox, Travell and Molofsky in their case²⁰ Once the "critical shortening" of the P-R interval is reached, the normal P-R interval may increase still further without affecting the anomalous QRS interval In these circumstances, depolarization of the ventricles would take place wholly through the anomalous route This is actually suggested by the shortening of the P-R peak interval while the QRS interval lengthens (table 3) If this reasoning is correct, it explains the failure of digitalis to lengthen the QRS interval in case 36, before digitalization the P-R difference was in the critical zone, and depolarization was wholly anomalous, and therefore unaffected by increase in the normal P-R interval A simpler explanation is that the normal P-R interval did not increase under the effect of digitalis, but this is unlikely

SUMMARY

Analysis of our 52 cases (11 old and 41 new) indicates that the syndrome of short P-R interval, wide QRS waves and paroxysmal tachycardia occurs most commonly in young people, more often in males than in females and in healthy persons from early childhood to old age Paroxysmal tachycardia occurred in 70 per cent of the patients It is compatible with good health and strenuous activity and does not predispose to the development of heart disease, although congestive failure rarely may result from prolonged, uncontrolled tachycardia Except for symptoms due to paroxysmal tachycardia, and rare instances of sudden death, none of which occurred in our cases, the abnormal mechanism is asymptomatic and does not affect the prognosis in cases of intercurrent disease, surgical procedures or pregnancy, and does not affect longevity

The abnormal electrocardiogram is frequently misinterpreted, leading to a mistaken diagnosis of serious heart disease or of paroxysmal ventricular tachycardia Methods of avoiding this error, as well as the many procedures for altering the abnormal electrocardiogram, which are helpful in interpretation, are discussed

The accumulated evidence clearly favors, but does not conclusively prove, an accessory conducting pathway as responsible for the disordered cardiac mechanism Such a pathway, with a short conduction interval, would make possible the premature depolarization of part of the ventricular muscle, and offers a possible explanation for paroxysmal tachycardia In some cases excitation of ventricular muscle also proceeds through the normal pathways, and in such instances the sum of the P-R and QRS intervals is the same for the normal and the abnormal beats

20 Fox, T T, Travell, J, and Molofsky, L Action of Digitalis on Conduction in the Syndrome of Short P-R Interval and Prolonged QRS Complex, *Arch Int Med* 71 206 (Feb) 1943

In other cases the sum of these intervals is not identical, and at least in some of these cases depolarization of the ventricular muscle takes place wholly through the anomalous route. One of the factors which determines whether or not the QRS complex represents an interference phenomenon or depolarization wholly through the anomalous route is the degree of shortening of the anomalous P-R interval. The critical value depends on many factors but is probably close to 0.08 second.

The anomalous QRS and P-J intervals usually do not exceed 0.14 and 0.26 second, respectively, values in excess of these figures do not necessarily indicate independent heart disease.

Digitalis may or may not widen the anomalous ventricular complex, a possible explanation is suggested. In a case of auricular fibrillation with anomalous QRS waves, digitalis was ineffective in controlling the ventricular rate.

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Progress In Internal Medicine

INFECTIOUS DISEASES

Fourteenth Annual Review of Significant Publications

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THE GREAT DECLINE in the incidence of infectious diseases and in the death rate among patients with such diseases in the past fifty years is an obvious fact. In a calculation of the mortality rate among policy holders of a large life insurance company,¹ new low rates in 1947 are reported for whooping cough, diphtheria, influenza, pneumonia, tuberculosis, syphilis and appendicitis. For pneumonia alone the death rate has declined 70 per cent since 1937, when chemotherapy, soon followed by antibiotic therapy, began to be used generally. There is nothing at present which threatens to stem the downward trend to what eventually will be an irreducible minimum. According to Gordon,² who discusses the influence of disease in war, the ratio of death from disease to deaths in battle gradually and irregularly declined from 7:1 in the Mexican War of 1846 to 0.4:1 in World War I to 0.01:1 in the last war. In Ingraham's opinion³ the death rate from infectious disease is now one fortieth of what it was fifty years ago. So far as morbidity is concerned, rheumatic fever, poliomyelitis and minor infections of the respiratory tract still resist efforts to control them.

These gratifying results of modern preventive and therapeutic measures are bound to affect the general nature of the practice of medicine. The decline of importance of infectious disease may be indicated in the substance of papers presented at national medical meetings last spring unless the selection of titles reflects the interests and choice of those who arranged the programs. For example, of the twenty-eight papers presented before the American Society of Clinical Investigation, only five dealt

From the Jefferson Medical College

1 Mortality Decline to New Low in 1947, *Statist. Bull. Metrop. Life Insur. Co.* **29** 1-4 (Jan.) 1948

2 Gordon, J. E. The Strategic and Tactical Influence of Disease in World War II, *Am. J. M. Sc.* **215** 311-326 (March) 1948

3 Ingraham, H. S. Recent Advances in Communicable Disease Control, *New York State J. Med.* **48** 1135-1141 (May 15) 1948

specifically with infectious disease, and of thirty-four papers read at the Association of American Physicians, again only five were about infections. On the programs of both the Section on Internal Medicine and the Section on General Practice of the American Medical Association meeting only two of eighteen papers of each group concerned infectious diseases, and on the program of the General Scientific Meetings there were none. Lest a too complacent attitude ensue, it is well to bear in mind certain possibilities for the future. One is the maturation of a population unimmune to many serious infections by reason of lack of exposure to them, which even in normal circumstances may be liable to unexpected epidemics of local origin. Another is the ever present chance of the introduction of some common or exotic disease from regions in the world in which hygienic and economic conditions are still primitive as illustrated by an epidemic of smallpox described on a later page. Finally, the sudden destruction of cities by new agents of warfare would reduce communities to primitive conditions and provide fertile fields for epidemic infections among the survivors. It is probable that biologic warfare against man will be successful only under such conditions.

Exotic Diseases—Unless they are often unrecognized or case reports are not always published, there have been surprisingly few exotic infectious diseases among veterans who served in areas in which kala-azar, leprosy, melioidosis, trypanosomiasis, schistosomiasis and other conditions were endemic.⁴ In describing such instances, authors often wrongly use the term "incubation period" to name the long time between the original infection and the onset of symptoms. Micro-organisms hardly "incubate" for months or years. In many instances the circumstance is more aptly named the carrier state. The incubation period begins when the agent becomes invasive and arbitrarily ends when the agent begins to cause overt trouble.

ANTIBIOTICS

Penicillin—Too much importance has been given to the need for maintaining a persistently large amount of penicillin in the blood. As Eagle points out,⁵ the amount in the blood is significant only in so far as the blood carries penicillin to the site of infection in the tissues. The amount attained and held in the tissue is the important factor. In general, except for walled off, relatively avascular foci, enough penicillin reaches infected areas if between two and ten times the necessary amount is present in the blood. Penicillin may be inactivated and also reversibly

4 Exotic Disease, editorial, J A M A 136 111-112 (Jan 10) 1948

5 Eagle, H. Speculation as to the Therapeutic Significance of the Penicillin Blood Level, Ann Int Med 28 260-278 (Feb) 1948

bound by the tissues. Slow dissociation of penicillin bound to the protein of cells would seem to permit local activity much longer than might be suspected from its rapid disappearance in the blood.⁶ Large amounts of penicillin obviously are more effective than small ones because they provide killing concentrations over a longer time.

Since 1944, Price⁷ has treated patients with pneumonia by injecting penicillin in doses of 100,000 units twice daily. When indicated, 200,000 units were given intravenously initially. The results obtained were equal to those obtained after injections at shorter intervals. Similar good results are reported from the treatment of mice with streptococcic infections once or twice a day.⁸ Other tests⁹ showed that penicillin inhaled in the nebulized form by animals is present in decreasing amounts as far as the bronchioles. In no case was penicillin found in the alveoli. These experiments give no support for the treatment of pulmonary infections by the inhalation of penicillin. Opposite results are reported by others,¹⁰ who surprisingly found both penicillin and streptomycin in "the lungs" of rats in far greater amounts after inhalation than after intramuscular injection of similar or even larger doses. Penicillin appeared in the blood after inhalation, streptomycin did not. The matter is unsettled and requires further study.

To take the place of the widely advertised but unsatisfactory penicillin-beeswax-peanut oil preparation, a new compound, procaine penicillin G, has been devised.¹¹ The substance was first prepared with cottonseed oil but is now made for aqueous suspension. It is slowly absorbed, and an intramuscular injection of 300,000 units provides therapeutically

6 Schachter, R. J. Fate and Distribution of Penicillin in the Body. I. Circulation of Penicillin in the Lymph, *Proc Soc Exper Biol & Med* **68** 29-34 (May) 1948

7 Price, A. H. Aqueous Penicillin Therapy for Pneumococcic Pneumonia. Injection at Twelve Hour Intervals, *J A M A* **138** 292-293 (Sept 25) 1948

8 White, H. J., Baker, M. J., and Jackson, E. R. Therapeutic Effectiveness of Single and Divided Doses of Penicillin in a Streptococcal Infection in Mice, *Proc Soc Exper Biol & Med* **67** 199-203 (Feb) 1948

9 Sloan, J. Q., Bain, G. P., and Brucer, M. Depth of Penetration of Nebulized Substances in the Respiratory Tree, *Proc Soc Exper Biol & Med* **66** 264-267 (Oct) 1947

10 Laurant, A. M., McIlroy, A. P., and Hadley, F. P. Penicillin and Streptomycin in the Lungs and Blood Serum of Rats Following Inhalational and Intramuscular Administration, *Proc Soc Exper Biol & Med* **68** 213-216 (May) 1948

11 Procaine-Penicillin G (Duracillin). A New Salt of Penicillin Which Prolongs the Action of Penicillin, *Proc Staff Meet, Mayo Clin* **22** 567-570 (Dec 10) 1947. Sullivan, N. P., Symmes, A. T., Miller, H. C., and Rhodehamel, H. W., Jr. A New Penicillin for Prolonged Blood Levels, *Science* **107** 169-170 (Feb 13) 1948

effective amounts in the body for twenty-four to thirty hours¹² Sensitivity to procaine in certain persons must be anticipated

Enormous amounts of penicillin were used in a case of subacute bacterial endocarditis caused by *Streptococcus fecalis* resistant to 6 to 12 units of penicillin Hagedorn and Scheifley¹³ gave 10,000,000 units daily for a period and over 300,000,000 units in fifty-six days Extensive bullous and fluctuant sterile necrotic areas developed at sites of injection, but the patient recovered

Barber¹⁴ fears, as others have, that the widespread use of penicillin is causing the appearance of many penicillin-resistant strains of staphylococci which in time may become the sole surviving ones Such penicillin-resistant strains may spread from person to person Of one hundred strains isolated from patients, thirty-eight were resistant

Efforts are under way to determine the need for substances which retard the rapid excretion of penicillin In one study¹⁵ caronamide, a substance which accomplishes this purpose, caused a severe reaction It is questionable, except in unusual cases, if such drugs are needed

Miller¹⁶ publishes further data on the superior efficacy of crude penicillin over the crystallized form in the protection of mice against certain bacterial toxins

Streptomycin —A rare fatal case of encephalopathy, probably caused by streptomycin given intramuscularly in a total dose of 15.6 Gm for five days, is reported¹⁷ The patient had had renal disease, and 256 micrograms per cubic centimeter of streptomycin accumulated in the blood A nurse who had handled streptomycin but had never received it had a severe anaphylactic reaction to an intracutaneous test dose of 0.05 cc (500 units)¹⁸

12 Hobby, G. L., Brown, E., and Patelski, R. A. Biological Activity of Crystalline Procaine Penicillin in Vitro and in Vivo, *Proc Soc Exper Biol & Med* 67 6-14 (Jan) 1948

13 Hagedorn, A. B., and Scheifley, C. H. Subacute Bacterial Endocarditis A Case Report, *Proc Staff Meet, Mayo Clin* 23 14-16 (Jan 7) 1948

14 Barber, M. Staphylococcal Infection Due to Penicillin-Resistant Strains, *Brit M J* 2 863-865 (Nov 29) 1947

15 Vander Veer, J. B., and Richardson, F. M. Penicillin Plus Caronamide in the Treatment of Subacute Bacterial Endocarditis, *Tr & Stud, Coll Physicians, Philadelphia* 15 109-112 (Dec) 1947

16 Miller, C. P., Hawk, W. D., and Boore, A. K. Protection Against Bacterial Endotoxins by Penicillin and Its Impurities, *Science* 107 118-119 (Jan 30) 1948

17 Hunnicutt, T., Graf, W. J., Hamburger, M., Ferris, E. B., and Scheinker, I. M. Fatal Toxic Encephalopathy Apparently Caused by Streptomycin, *JAMA* 137 599-602 (June 12) 1948

18 Rosen, F. L. Sensitivity to Streptomycin Anaphylactic Shock with Recovery Following an Intracutaneous Test, *JAMA* 137 1128 (July 24) 1948

Further study has been made of bacteria which require streptomycin for growth. Such variant forms have been found among *Escherichia*, *Pseudomonas aeruginosa*, *Bacillus subtilis*,⁷ *Staphylococcus* and *Proteus morganii*.

NEW ANTIBIOTIC AGENTS

According to Florey,²⁰ several hundreds of fungi and many bacteria produce antibacterial substances. Much work is being done to evaluate the few antibiotics which promise to be of therapeutic value and to discover others.

Two newly developed, chemically different antibiotic agents, polymyxin and aerosporin, were derived from similar bacteria. Polymyxin was better than streptomycin in controlling infections in animals caused by *Klebsiella pneumoniae*, *Hemophilus influenzae*, *Hemophilus pertussis* and *Neisseria intra-cellularis*.²¹ The acute toxicity of polymyxin for animals is greater than that of penicillin or streptomycin. Several patients with infections caused by *P. aeruginosa*, *K. pneumoniae*, *H. pertussis* and *Bacillus abortus* were successfully treated.

Brownlee and Bushby²² find aerosporin to be of greater value than polymyxin for many infections caused by gram-negative bacilli. Aerosporin was successfully used in 10 children with pertussis.²³

Chloromycetin obtained from a soil actinomycete²⁴ was effective in the treatment of mice infected with scrub typhus and psittacosis.²⁵ The agent was also of value in the treatment of 25 patients with scrub typhus.

19 Kushnick, T., Randles, C. I., Gray, C. T., and Birkeland, J. M. Variants of *Escherichia Coli*, *Pseudomonas Aeruginosa* and *Bacillus Subtilis* Requiring Streptomycin, *Science* **106** 587-588 (Dec. 12) 1947. Paine, T. F., and Finland, M. Streptomycin-Sensitive, -Dependent and -Resistant Bacteria, *ibid.* **107** 143-144 (Feb. 6) 1948.

20 Florey, H. New Antibiotic Agents, *J. A. M. A.* **135** 1047-1049 (Dec. 20) 1947.

21 Schoenbach, E. B., Bryer, M. S., Bliss, E. A., and Long, P. H. Polymyxin. A Note on Experimental and Clinical Investigation, *J. A. M. A.* **136** 1096-1098 (April 24) 1948.

22 Brownlee, G., and Bushby, S. R. M. Chemotherapy and Pharmacology of Aerosporin. Selective Gram-Negative Antibiotic, *Lancet* **I** 127-133 (Jan. 24) 1948.

23 Swift, P. N. Treatment of Pertussis with Aerosporin, *Lancet* **I** 133-134 (Jan. 24) 1948.

24 Ehrlich, J., Bartz, Q. R., Smith, R. M., and Joslyn, D. A. Chloromycetin, a New Antibiotic from a Soil Actinomycete, *Science* **106** 417 (Oct. 31) 1947.

25 Smadel, J. E., and Jackson, E. B. Chloromycetin, an Antibiotic with Chemotherapeutic Activity in Experimental Rickettsial and Viral Infections, *Science* **106** 418-419 (Oct. 31) 1947.

in Malaya²⁶ Ten patients with typhoid were greatly benefited by chloromycetin given orally²⁷

Aureomycin is effective against a wide range of gram-positive and gram-negative bacilli^{27a} Experimental infection with rickettsias and agents of the psittacosis group are also controlled Like chloromycetin, it is given orally Aureomycin was used with success for brucellosis and in several cases of pneumococcic pneumonia^{27b} Toxic effects were not serious

Bacillus subtilis has yielded several antibiotic agents—subtilitin, bacitracin, bacillin, subtenolin and bacillomycin Each has a spectrum of activity against different bacteria or fungi Subtenolin²⁸ is active against both gram-positive and gram-negative bacteria, and bacillomycin²⁹ is fungistatic for almost all the important dermatophytes and fungi causing systemic disease Results of tests on animals and clinical trial are awaited with interest

As yet no antibiotic agent has been discovered to be effective against filtrable viruses

DISEASES OF THE RESPIRATORY TRACT

It is estimated³⁰ that colds and related diseases cost Americans about a billion dollars a year, including four hundred million for drugs and medical care and the rest for loss in wages

In a three year study³¹ of diseases of the respiratory tract in an army post it was found that viral pneumonias were present in 5 to 10 per cent

26 Smadel, J E , Woodward, T E , Levy, H L , Jr , Philip, C B , and Traub, R Chloromycetin in the Treatment of Scrub Typhus, *Science* **108** 160-161 (Aug 13) 1948

27 Woodward, T E , Smadel, J E , Ley, H L , Jr , Green, R , and Manlikar, D S Effect of Chloromycetin in the Treatment of Typhoid Fever, *Ann Int Med* **29** 131-134 (July) 1948

27a Finland, M , Collins, H S , and Paine, T F Aureomycin, a New Antibiotic Results of Laboratory Studies and of Clinical Use in Cases of Bacterial Infections, *J A M A* **138** 946-949 (Nov 27) 1948

27b Collins, H S , Paine, T F , and Finland, M Aureomycin in Treatment of Pneumonia and Meningococcemia, *Proc Soc Exper Biol & Med* **69** 263-265 (Nov) 1948

28 Hirschhorn, H N , Bucca, M A , and Thayer, J D Subtenolin An Antibiotic from *Bacillus Subtilis*, I Bacteriologic Properties, *Proc Soc Exper Biol & Med* **67** 429-432 (April) 1948

29 Landy, M , Warren, G H , Rosenmann, S B , and Colio, L G Bacillomycin An Antibiotic from *Bacillus Subtilis* Active Against Pathogenic Fungi, *Proc Soc Exper Biol & Med* **67** 539-541 (April) 1948

30 Cost of the Common Cold, *Statist Bull Metrop Life Insur Co* **28** 6-7 (Nov) 1947

31 Clinical Patterns of Undifferentiated and Other Acute Respiratory Diseases in Army Recruits, Commission on Acute Respiratory Diseases, *Medicine* **26** 441-464 (Dec) 1947 , Bacteriological Findings in Undifferentiated and Other Acute Respiratory Diseases, Commission on Acute Respiratory Diseases, *ibid* **26** 465-484 (Dec) 1947

of cases and bacterial pneumonias in 2 per cent. An undefined syndrome called acute respiratory disease (ARD) comprised 75 to 90 per cent of the minor diseases and exudative tonsillitis and pharyngitis 10 to 15 per cent, of which half were caused by beta hemolytic streptococci. Influenza occurred only sporadically, and the common cold (acute coryza) is not discussed although it is believed to be a different disease. One wonders if the common cold was not encountered over the three year period or if it was excluded from consideration because the patients were ambulatory and not studied in the hospital as the rest were. In another study, published last year and again in December 1947,³² mild undifferentiated diseases of the respiratory tract were regarded as representing a spectrum of overlapping entities, with the common cold at one end, acute respiratory disease (ARD) in the middle and the syndrome including viral pneumonia at the other end. The reader cannot tell if nonbacterial, exudative pharyngitis previously described by the authors is excluded from the list or grouped with acute respiratory disease (ARD). According to tests in volunteers, the common cold, (ARD) and viral pneumonia are immunologically different. In papers on this and other subjects the words "human volunteers" are often used, one wonders what other kind there are.

In the largest experiment ever conducted on the common cold, Andrewes³³ has not yet succeeded in cultivating the causative agent. The virus particles were found to measure 0.0001 mm., about the same as those of influenza virus. The virus resists freezing at -70°C .

Topping and Atlas³⁴ apparently succeeded in cultivating a virus of one of the group of minor ailments of the respiratory tract in the chick embryo. Among 60 volunteers inoculated with the culture symptoms like those of the donor of the virus developed in 57. The incubation period varied from seven to twenty-four hours, and the disease sometimes lasted eleven days, with nasal obstruction, rhinorrhea, sneezing, cough and headache. The lymphoid follicles of the pharynx were prominent and the nasal membrane hyperemic. Fever occurred in only 12. When subjected to electromicroscopy, supposedly infected allantoic fluids showed particles of the same size as those of influenza virus but different from them, while no particles were seen in noninfected fluid. As in the experiments on viral dysentery carried out by my colleagues and me, similar symptoms developed in 25 to 50 per cent of volunteers given uninfected inoculums, which likewise clouds the issue.

32 Dingle, H. H. Experimental Studies of the "Common Cold" in Human Volunteers, *Tr. & Stud. Coll. Physicians, Philadelphia* 15: 113-123 (Dec.) 1947.

33 Research on the Common Cold, *Foreign Letters, JAMA* 136: 277 (Jan. 24) 1948.

34 Topping, N. H., and Atlas, L. T. The Common Cold. A Note Regarding Isolation of an Agent, *Science* 106: 636-637 (Dec. 26) 1947.

Calvy³⁵ describes three epidemics of colds on a ship at sea, in each of which numbers of patients, 18 in all, had symptoms and signs of acute appendicitis. Rhinorrhea was present in 16 cases, but fever was present in only 3. The laboratory data generally indicated no abnormalities. Appendectomy was performed in 12 instances when symptoms of appendicitis persisted. The rest of the patients were regarded as having mesenteric lymphadenitis. All the appendixes examined were acutely inflamed, and plastic fibrinous exudate was present in 7. Mesenteric lymphadenitis was noted in 3 cases. The observations suggest a relation between certain forms of epidemic infection of the respiratory tract and acute appendicitis. Appendicitis may not be always of bacterial origin.

A disease of dogs called pharyngolaryngotracheitis was transmitted to other dogs but not to mice with filtered secretion, which suggests that a virus was the cause.³⁶

Pneumonia—The great diminution in the incidence of pneumococcal lobar pneumonia and in the mortality from it is reflected in the paucity of papers on the subject in the past few years as compared with those which appeared in the presulfonamide era. A few have appeared. One is surprised to learn from Collen's paper³⁷ that there were as many as 2,176 patients with the disease in one hospital in salubrious California in a three year period. Particular interest is devoted to type III pneumococcal pneumonia as the one causing the highest mortality rate, 34 per cent, in spite of therapy with sulfadiazine. Although penicillin reduced the rate to 4.3 per cent, it was still higher than that of any other type.

From similar studies, Israel and his co-workers³⁸ report a reduction in mortality rate of lobar pneumonia from 23 per cent in 1937 to 6.5 per cent in 1946. In general they report a trend in the characteristics of pneumonia away from the typical form, often so much so that it causes confusion with the viral pneumonias. They report the leukocyte count to be generally lower and the response to therapy slower than in previous years. It is unfortunate that the causative pneumococci were not "typed" in the latter years of their study. It would seem that a diminution in recent years of the number of cases of pneumococcal pneumonias types I and II, which are the most "typical" of the forms of pneumonia, may account largely for this change. If the proportion of

35 Calvy, G. L. Appendicitis and Upper Respiratory Infection. A Report of Eighteen Cases at Sea, *Ann. Int. Med.* **28**: 998-1002 (May) 1948.

36 Gustafsen, W. E. Preliminary Studies on the Agent of Canine Pharyngo-Laryngo-Tracheitis, *Yale J. Biol. & Med.* **20**: 185-196 (Dec.) 1947.

37 Collen, M. F., and Dobson, R. L. Clinical Evaluation of the Treatment of Pneumococcal Type III Pneumonia, *Am. J. Med.* **4**: 383-389 (March) 1948.

38 Israel, H. L., Mitterling, R. C., and Flippin, H. L. Pneumonia at the Philadelphia General Hospital, 1936-1946, *New England J. Med.* **238**: 205-212 (Feb. 12) 1948.

cases of pneumonia of types I and II has been reduced generally throughout the country, I would suspect it to be the result of prompt control of infections as they arise with sulfonamide drugs or penicillin and the consequent reduction of pneumococci which would otherwise be spread to cause infection in others

In Israel's series in 1945 to 1946 there were 312 cases of lobar pneumonia and only 14 cases of viral pneumonia listed. This is in striking contrast with other reports. In Horsfall's series,³⁹ consisting of a military group of 6,000 persons, 250 had pneumonia, and in only 6 cases were bacteria thought to be the cause. In another army post viral pneumonias were three to five times as numerous as bacterial pneumonias. In my own service in the winter of 1948 there were 15 cases of pneumonia, only 1 of type I, and 4 of viral pneumonia, the smallest number ever dealt with.

A confusing paper^{39a} deals with the differentiation of influenza from viral pneumonia. The author perpetuates the meaningless term primary atypical pneumonia and consistently ignores certain opinions apparently not in accord with his own. No reference is made to the likelihood that epidemic viral pneumonia represents only the severest instances of mild widespread disease. In differentiation, he compares only the pneumonic forms (viral pneumonia) with all cases of influenza, both mild and pneumonic. Obviously, the incidence of the disease including viral pneumonia is made to appear much lower than that of influenza, which was not so during the war years, other differences also are exaggerated. Pulmonary consolidation in viral pneumonia is described, but consolidation in its strict sense almost never occurs.

Necropsy in 8 cases of viral pneumonia disclosed no new facts.⁴⁰ Two of the cases were of erythema multiforme exudativum and 1 may have been a case of psittacosis. In another instance a woman handled a sick English sparrow, and two weeks later psittacosis developed. Sparrows were then tested for evidence of psittacosis (ornithosis), but no evidence of natural infection was found.⁴¹ Sparrows were infected experimentally by intracerebral inoculation and by being fed with the virus.

39 Treatment of Pneumonia, Conference on Therapy, *Am J Med* 4 423-435 (March) 1948

39a Horsfall, F L Primary Atypical Pneumonia and Influenza, *Bull New York Acad Med* 24 431-446 (July) 1948

40 Parker, F, Jolliffe, L S, and Finland, M Primary Atypical Pneumonia. Report of Eight Cases with Autopsies, *Arch Path* 44 581-608 (Dec) 1947

41 Davis, D J Susceptibility of the English Sparrow (*Passer Domesticus*) to Infection with Psittacosis Virus of Pigeon Origin, *Proc Soc Exper Biol & Med* 66 77-79 (Oct) 1947

In agreement with my view, Scadding⁴² rejects the term primary atypical pneumonia as unsatisfactory on factual and logical grounds

Unusual Forms of Pneumonia—Finland⁴³ reports 4 cases of erythema multiforme exudativum with pneumonia, 3 of them fatal In 2 instances psittacosis-like virus may have been operative and in a third herpes virus The pneumonia closely resembled viral pneumonia Certain observers⁴⁴ still regard the dermal lesions as a complication of viral pneumonia instead of part of a separate entity

Twenty-six soldiers who spent some time in an abandoned cellar in Oklahoma had pneumonia eight to eighteen days afterward, in 20 it was severe, in 2 moderately severe and in 4 mild⁴⁵ The disease was regarded as an unusual one, different from the oft described viral pneumonia, but all the signs and symptoms were identical with those of the disease as first described in 1938 Q fever apparently was not considered as a diagnosis

From a study of an outbreak of 58 cases of viral pneumonia in Naples in March 1946, Stephens⁴⁶ suggests a relationship to viral hepatitis on the weak evidence of an occasionally palpable liver The disease, he admits, may have been Q fever

In 1936, 1940 and 1947 European physicians, Fanconi, Hegglin and Gasser respectively, reported a new entity, "Wassermann-positive" pneumonia⁴⁷ It occurs in epidemic form and is presumably caused by a virus They regard the transient serologic reaction to be dependent on an increased amount of globulin The sedimentation rate is increased, but no cold agglutination of erythrocytes occurs

Influenza—According to Finland and his associates,⁴⁸ an epidemic of influenza B broke out in Boston in December 1945 Influenza B disappeared in early January, but after that time influenza A appeared

42 Scadding, J G The Pneumonias Associated with Epidemic Respiratory Infections, *Lancet* **1** 89-93 (Jan 17) 1948

43 Finland, M, Jolliffe, L S, and Parker, F Pneumonia and Erythema Multiforme Exudativum, *Am J Med* **4** 473-492 (April) 1948

44 Knutsen, B Primary Atypical Pneumonia, *Norsk mag f lægevidensk* **36** 2099-2105 (Oct 17) 1947

45 Cam, J C, Devins, E J, and Downing, J E An Unusual Pulmonary Disease, *Arch Int Med* **79** 626-641 (June) 1947

46 Stephens, J W Primary Atypical Pneumonia, *Lancet* **1** 703-707 (May 8) 1948

47 Gasser, C Wassermann-Positive Bronchopneumonia During Childhood and Its Various Manifestations (Fanconi-Hegglin Syndrome) Contribution to Aspects of Military Bronchopneumonia and Virus Pneumonia, *Helveti pædiat acta* **2** 185-226 (June) 1947

48 Finland, M, Barnes, M W, Meads, M, and Ory, E M Serologic Studies of Influenza Made in Boston During the Winter of 1945-1946, *J Lab & Clin Med* **33** 15-31 (Jan) 1948

Two patients were observed who had influenza B followed in a few weeks by influenza A. Evidence of symptomless infections also appeared. Certain patients who had what appeared to be influenza failed to show serologic evidence of either A or B infection. Most of those who failed to show a rise of antibody titer had what seemed to be other minor infections of the respiratory tract. There was evidence of at least two antigenically different B strains active in the epidemic.⁴⁹

During the epidemic of influenza B, 69 cases of pneumonia were studied.⁵⁰ In about half of the cases there was serologic evidence of infection with the B virus, and in almost all of these there was a history of disease characteristic of influenza a few days before or at the onset of pneumonia. The pneumonias were about the same in nature whether preceded by influenza or not. Similar observations had been made previously by others in regard to influenza A.

Four more reports,⁵¹ in addition to those mentioned in last year's review, describe the failure of influenza vaccine to prevent outbreaks of influenza caused by an A virus slightly different immunologically from the A virus used as vaccine. If vaccine against influenza is ever to be successful, one must do several things: (a) prepare a vaccine able to give a higher antibody response, (b) use adjuvants with vaccine to increase the antibody response, (c) immunize a group before or soon after a known outbreak has been reported elsewhere or (d) make vaccine with the strains causing an outbreak, but because of the time involved it is seldom possible to prepare this quickly enough.

In another study similar observations were made. Under apparently ideal conditions in the army, in which accurate reporting of cases is made, forewarning of anticipated outbreaks of influenza A in various posts was made possible by early recognition of the beginning of an outbreak in 1947. Accordingly, vaccine was immediately sent to posts as yet unaffected, but even then its use did not prevent the disease. The failure

49 Barnes, M. W., Morgan, H. R., and Finland, M. Isolation and Identification of Influenza Viruses During Epidemic of December, 1945, *J. Lab. & Clin. Med.* **33** 309-318 (March) 1948.

50 Finland, M., Ory, E. M., Meads, M., and Barnes, M. W. Influenza and Pneumonia. Serologic Studies During and After an Outbreak of Influenza B, *J. Lab. & Clin. Med.* **33** 32-46 (Jan.) 1948.

51 Van Ravenswaay, A. C. Prophylactic Use of Influenza Vaccine. An Instance of Inadequate Protection Against Influenza A, *J. A. M. A.* **136** 435-437 (Feb. 14) 1948. Sigel, M. M., Shaffer, F. W., Wiener Kirber, M., Light, A. B., and Henle, W. Influenza A in a Vaccinated Population, *ibid.* **136** 437-441 (Feb. 14) 1948. Sartwell, P. E., and Long, A. P. The Army Experience with Influenza, 1946-1947. I. Epidemiological Aspects, *Am. J. Hyg.* **47** 135-141 (March) 1948. Kalter, S. S., Chapman, O. D., Feeley, D. A., and MacDowell, S. L. An Epidemic of Influenza Due to an Atypical Strain. The Relationship of This Strain to Other Influenza Viruses, *J. Immunol.* **59** 147-157 (June) 1948.

might be ascribed to the lack of time required for immunity to develop or, more likely, as mentioned in the preceding paragraph, to the operation of a different antigenic strain of virus ⁵²

Information along this line accrues from Hirst's⁵³ observations on influenza viruses. Virus A may cause "full-blown influenza infection" and maximum multiplication in the mouse lung without gross evidence of pathologic change. By passage through mice, enhancement of virulence occurs not by a steplike increase with each passage, as once believed, but by the abrupt appearance of a new form of virus with the same ability to grow but with a different pathogenic habit which replaces the original form. The new "virulent" form appears to be established after four or five passages, during which the virulence levels off and remains fixed, unless, of course, other new and even more pathogenic variants appear. Most observations, however, indicate that during epidemics the causative virus is uniform and stable. Changes appear during laboratory manipulation. Variations in antigenic pattern of viruses during passage occur which may cause a virus to become different from the original form. For example, two similar strains on passage may come to differ with their original pattern and even from each other ⁵⁴

Such changes may explain the O and D phenomenon of Burnet, the O form being present in initial isolation but being replaced by the D form, which is therefore the one commonly dealt with in laboratories. Adaptation of human virus to egg medium is a less drastic procedure than adaptation to mice and causes less antigenic difference. Magill and Sugg⁵⁵ confirm Burnet's observation of a change from the O to the D form of influenza virus during artificial cultivation. The change, however, is reversible and resembles the phase variation of bacteria. It is obvious that influenza viruses are as unstable as other micro-organisms, and the sudden changes in character of viruses are thus explained.

A practical conclusion from these observations and from those previously discussed indicates that vaccines, to be effective, should be made with strains of virus antigenically similar to the one or ones causing a current epidemic. Vaccine obtained from egg-adapted strains would seem to be preferable. It is recommended⁵⁶ that all strains of the influenza

52 Rasmussen, A. F., Stokes, J. C., and Smadel, J. E. The Army Experience with Influenza, 1946-1947. II. Laboratory Aspects, *Am J Hyg* **47** 142-149 (March) 1947.

53 Hirst, G. K. Studies on the Mechanism of Adaptation of Influenza Virus to Mice, *J Exper Med* **86** 357-366 (Nov) 1947.

54 Hirst, G. K. Comparisons of Influenza Virus Strains from Three Epidemics, *J Exper Med* **86** 367-381 (Nov) 1947.

55 Magill, T. P., and Sugg, J. Y. The Reversibility of the O-D Type of Influenza Virus Variation, *J Exper Med* **87** 535-546 (June) 1948.

56 Center for Study of Influenza Virus Strains Established, Current Comment, *J A M A* **135** 1156 (Dec 27) 1947.

virus isolated in the future be submitted to the Influenza Virus Strain Study Center at 1300 York Avenue, New York city, for classification so that strains of current importance may be promptly identified

The intradermal inoculation of small amounts, 0.02 cc., of concentrated influenza A and B vaccine evokes as much antibody response as that which follows the subcutaneous injection of 1 cc. of the usual form of vaccine.⁵⁷ Immediate and delayed mild dermal reactions and mild systemic reactions were common. In a group of persons, some of whom were vaccinated by this method, the incidence of infections of the upper respiratory tract was not significantly different.

The complement fixation test is better than the Hirst chicken red cell agglutination test for the serologic diagnosis of epidemic influenza.⁵⁸ It is species specific and differentiates A and B virus but is not strain specific like the Hirst test.

VIRUSES

Enders⁵⁹ comments on the great number of "new" diseases caused by viruses recognized since 1930, at which time it seemed to some as if etiologic discovery in this field was in its final stage. As examples of newly recognized diseases he cites viral pneumonias, viral dysentery, keratoconjunctivitis, Fort Bragg (pretibial) fever, Dodds's stomatitis and diarrhea, Colorado tick fever and a number of encephalitides, to which one may add viral hepatitis, viral myocarditis and perhaps amicrobic pyuria. Viruses, therefore, attack the eyes, lungs, heart, liver, intestinal tract and probably the kidneys in addition to the previously known sites of invasion.

Some years ago Andrewes tested one hundred and fifteen compounds for their possible therapeutic effect on viral infections without finding any to be of value. Similar disappointing studies are now reported by Cutting.⁶⁰ In discussing the meager progress made along these lines, Rivers⁶¹ notes that each of the few substances thus far shown to give promise of value only retards the multiplication of viruses and rickettsias. Bacteria and treponemes are killed by certain chemotherapeutic agents.

57 Weller, T. H., Cheever, F. S., and Enders, J. F. Immunologic Reactions Following the Intradermal Inoculation of Influenza A and B Vaccine, *Proc Soc Exper Biol & Med* **67** 96-101 (Jan) 1948

58 Hoyle, L., and Fairbrother, R. W. Serologic Diagnosis of Epidemic Influenza by Complement-Fixation Reaction, *Brit M J* **2** 991-993 (Dec 20) 1947

59 Enders, J. F. A Review of Some Recently Defined Virus Diseases, *New England J Med* **237** 897-900 (Dec 11) 1947

60 Cutting, W. C., and others. Chemotherapy of Virus Infections, *J Immunol* **57** 379-390 (Dec) 1947

61 Rivers, T. M. Recent Advances in the Treatment of Viral and Rickettsial Diseases, *J A M A* **136** 291-292 (Jan 31) 1948

because they have enzyme systems of their own with which various drugs interfere. Viruses and rickettsias as intracellular parasites are believed to have no enzyme system essential to growth and to depend on the host for survival and growth. If this is so, the failure of the present chemotherapeutic agents is explained. To questions raised during discussion Rivers answered that there is no successful specific prophylaxis for serum jaundice, poliomyelitis and the common cold.

In a symposium on viruses and viral diseases published in *The Journal of the American Medical Association* on April 24, 1948, Schulz reviews the knowledge of viruses which has accrued since Beijerinck first found a pathogenic filtrable agent fifty years ago. Smadel outlines the tests of practical and academic value for the diagnosis of viral diseases, Wycoff discusses electron microscopy of virus and Dingle again gives the views of the Commission on Acute Respiratory Diseases which have already been published in a number of places. Finally, Francis reports that in a search for extrahuman sources, the virus of poliomyelitis was sought in 15,300 specimens from various animals, fowl and flies and in sewage, sludge, soil, water and milk. All attempts to find the virus failed except in one collection of *Sarcophaga* flies.

With the use of a new approach to immunologic research with radioactive virus, tobacco mosaic virus injected into mice was found to accumulate chiefly in the liver, some collected in the spleen and the remainder elsewhere.⁶² The results suggest the liver to be important in the destruction or elimination of certain viruses.

Poliomyelitis—Intensive studies are still under way to learn which is the most important route of infection. Five epidemiologic reports were published. In one study⁶³ poliomyelitis virus was found in the throats of three children before they became sick with the disease. It was found to be present in the throat only for several days after in earlier tests, and epidemiologic studies by others indicate that transmission of the disease usually occurs within three to five days of the onset. From these facts it was argued that the chief source of the virus is the throat and that it is spread by contact or proximity. Even though the stools contain virus for weeks, they seem less likely to be a natural source of infection in the convalescent period. It still remains to be proved, however, that the virus in the feces is not equally dangerous in the transmission of the disease during the acute phase. In 1945 Francis reported the presence of virus in the feces of a patient nineteen days before an attack of poliomyelitis.

62 Radioactive Virus, editorial, *J A M A* 136 473 (Feb 4) 1948

63 Gordon, F. F., and others. Recovery of Poliomyelitis Virus from the Throat During the Incubation Period, *J A M A* 135 884-888 (Dec 6) 1947

In another study⁶⁴ on familial associates of patients with poliomyelitis about 23 per cent were revealed to be carriers. The number of carriers in a group, therefore, is equal to or twice as great as the number of actual patients and is not ten to one hundred times as great as was once thought. Virus may persist in stools of contact carriers for five weeks, or it may be intermittently present. Since carriers are found mostly among close contacts, public health measures had best be directed to family groups in which the disease occurs.

In the third study⁶⁵ 20 members of four households in which poliomyelitis occurred were studied. Virus was present in the feces of 16, and among these, 7 had virus in the oropharynx. Of 12 children, all had virus in their feces, and 5 had virus in the throat. It appeared, therefore, that all but 4 members of these families had poliomyelitis, but most of them had it in indefinite or abortive form. One may ask if they were not simply carriers. Two English physicians are at variance with each other. One⁶⁶ agrees with the views just expressed, namely, that the chief factor in the spread of poliomyelitis is human contact and the presence of virus in the nasopharynx is of much more importance in its spread than the presence of virus in the feces. The other⁶⁷ found no evidence of contact between paralytic patients, and no 2 patients came from the same military unit affected in an epidemic.

Loring and his co-workers,⁶⁸ who used concentrated preparations of poliomyelitis virus, were able to show complement-fixing antibodies in the blood of rats immunized with Lansing strain virus treated with "formol" and in some convalescent human serums. The results further support the relationship of the Lansing strain or related ones to human diseases, and the test may serve as an important diagnostic aid.

By the use of simple methods of purification, the virus of poliomyelitis on electromicroscopy was seen to be composed of uniform particles ranging from 10 to 20 millimicrons in diameter, usually 12 millimicrons.⁶⁹

64 Brown, G. C., Francis, T., and Ainslie, J. Studies of the Distribution of Poliomyelitis Virus. V. The Virus in Familial Associates of Cases, *J. Exper. Med.* **87** 21-27 (Jan.) 1948.

65 Wenner, H. A., and Tanner, W. A. Widespread Distribution of Poliomyelitis in Households Attacked by the Disease, *Proc. Soc. Exper. Biol. & Med.* **66** 92-95 (Oct.) 1947.

66 Sweetnam, W. P. Epidemiology of the 1947 Outbreak of Poliomyelitis in Eccles, *Brit. M. J.* **1** 1172-1175 (June 19) 1948.

67 Dixon, G. J. The Oecology of Poliomyelitis in a Military Camp in 1947, *Brit. M. J.* **1** 1175-1178 (June 19) 1948.

68 Loring, H. S., Raffel, S., and Anderson, J. C. Complement-Fixation in Experimental and Human Poliomyelitis, *Proc. Soc. Exper. Biol. & Med.* **66** 385-392 (Nov.) 1947.

69 Gallan, F., and Marvin, J. F. Electron-Microscopy of the Purified MM Poliomyelitis Virus, *Proc. Soc. Exper. Biol. & Med.* **67** 366-367 (March) 1948.

During an epidemic, a heretofore undescribed virus was encountered in the feces of children with poliomyelitis which caused paralysis and destructive lesions in the muscles of mice without affecting the central nervous system⁷⁰ Repeated recovery of the agent from feces and the immunologic response of patients suggested that the agent may be pathogenic for man Its relationship to the epidemic is undetermined

In an unsuccessful attempt to obtain information about the dangers of tonsillectomy in precipitating bulbar poliomyelitis, Cuning⁷¹ infers that the performance of tonsillectomy in cold seasons when poliomyelitis is not prevalent will increase the danger of infection of the respiratory tract To show how tenaciously certain ideas persist, he still writes that most tonsillectomies are necessary surgical procedures performed in the interest of preventive medicine There is, however, no reliable support for his statement, inherited from the past, that "infected" tonsils are etiologic foci of infection for nephritis, mastoiditis, rheumatic fever and "many other debilitating diseases"

Rubella and Pregnancy—According to studies in Australia⁷² of 760 stillbirths, infections of various sorts had occurred in the mothers, but rubella was the only one which gave a high incidence of injury to the embryo This conclusion is in agreement with earlier published reports

Impelled by the knowledge that rubella causes developmental defects of the fetus during the early stages of pregnancy, Hamburger and Habel⁷³ studied the viruses of influenza A and mumps as possible causes of teratogenic and lethal effects on early chick embryos As with rubella, the viruses of both caused developmental defects and were lethal at times, especially in early embryos Influenza virus affected the brain tissues in the embryo and the mucosa of the respiratory tract in later life

In Milwaukee between 1942 and 1945 Fox and his associates⁷⁴ interviewed as many women as possible who had measles, mumps or chickenpox Among infants conceived and born either before or after the mothers had had any one of those diseases the incidence of congenital anomalies was 0.9 per cent Of 33 live children born to women who had measles,

70 Dalldorf, G., and Sickles, G. M. An Unidentified, Filtrable Agent Isolated from the Feces of Children with Paralysis, *Science* **108** 61-62 (July 16) 1948

71 Cuning, D. S. Tonsillectomy and Poliomyelitis, *Arch Otolaryng* **46** 575-583 (Nov.) 1947

72 Swan, C. Rubella in Pregnancy as an Aetiological Factor in Stillbirth, *Lancet* **1** 744-746 (May 15) 1948

73 Hamburger, V., and Habel, K. Teratogenic and Lethal Effects of Influenza-A and Mumps Viruses in Early Chick Embryos, *Proc Soc Exper Biol & Med* **66** 608-617 (Dec.) 1947

74 Fox, M. K., Krumbiegel, E. R., and Teresi, J. L. Maternal Measles, Mumps and Chickenpox as a Cause of Congenital Anomalies, *Lancet* **1** 746-749 (May 15) 1948

mumps or chickenpox during pregnancy, only 1, whose mother had measles, had a harelip. The reports of others on women with rubella during pregnancy give a rate of anomalies of the infant as high as fifteen times the expected rate of 0.9 per cent. For poliomyelitis during the first four months of pregnancy, the incidence of anomalies is given as nine times the normal rate. The authors feel that the type of statistical approach by numerous observers has not given conclusive proof of the especially harmful effect of rubella on the fetus.

Herpes Simplex—A severe case of systemic infection and an exanthem of vesicles resembling variola was shown to be caused by the virus of herpes simplex⁷⁵

Evidence is accumulating⁷⁶ that the varicelliform eruption described by Kaposi is caused by the virus of herpes simplex in persons with atopic dermatitis. The virus was recovered from the lesions of 4 patients. The recovery of the virus distinguishes this infection from eczema vaccinatum caused by vaccine virus in patients with atopic dermatitis.

More evidence is published⁷⁷ that the virus of herpes simplex may reside in animals in the latent state and can be provoked into causing disease by an induced anaphylactic shock.

Smallpox—An epidemic of smallpox, similar to the one which occurred recently in New York city, was incited in England⁷⁸ by a soldier who arrived from India by air. He was first thought to have chickenpox, but soon after smallpox developed in 30 persons and 6 died. In a number of cases the disease developed nine to twelve days after vaccination.

Rabies—Rabies occurred in a child of 13 months without evidence of having been bitten by a rabid animal⁷⁹. His lip was cut accidentally five weeks before. The clinical course was unusual in that there was hyperexcitability alternating with sleep or coma and several days elapsed before dysphagia occurred. Diagnosis was made by the injection of saliva treated with penicillin intracerebrally into mice, the first time

75 Kipping, R. H., and Downie, A. W. Generalized Infection with the Virus of Herpes Simplex, *Brit. M. J.* **1**: 247-249 (Feb. 7) 1948.

76 Ruchman, I., Welsh, A. L., and Dodd, K. Kaposi's Varicelliform Eruption. Isolation of Virus of Herpes Simplex from Cutaneous Lesions of Three Adults and One Infant, *Arch. Dermat. & Syph.* **56**: 846-863 (Dec.) 1947.

77 Good, R. A., and Campbell, B. The Precipitation of Latent Herpes Simplex Encephalitis by Anaphylactic Shock, *Proc. Soc. Exper. Biol. & Med.* **68**: 82-87 (May) 1948.

78 Smith, C. S. Smallpox in Staffordshire, 1947. Outbreak at Bilston, *Brit. M. J.* **1**: 139-142 (Jan. 24) 1948.

79 Duffy, C. E., Woolley, P. V., Jr., and Nolting, W. S. Rabies. A Case Report with Notes on the Isolation of the Virus from Saliva, *J. Pediat.* **31**: 440-447 (Oct.) 1947.

that this has been accomplished Sellers,⁸⁰ from his thirty years of experience, writes that antirabies vaccine when given to persons who do not need it because of indirect or remote exposure has caused more deaths than has rabies itself In his series 3 persons died among 5 who were paralyzed by vaccine given mainly to allay apprehension Although the incidence of "treatment paralysis" as a complication of vaccination is only about 1 in 3,000, even this can be lowered by restricting the use of vaccine to those who need it Concise directions for procedure in persons exposed to rabies and indications for and against the use of vaccine are given in the paper

Derriengue, a highly fatal disease of cattle in western Mexico, is caused by a virus closely related to rabies virus and is transmitted by vampire bats⁸¹ The virus was recovered from cattle and bats The virus varies as much from rabies virus as do certain rabies viruses which have been altered in specificity by passage in experimental animals

It is almost impossible clinically to distinguish vesicular stomatitis from foot-and-mouth disease, but tests employing complement fixation suggest that they are different diseases and can be so diagnosed⁸²

Viral Hepatitis—Infectious jaundice, like homologous serum jaundice, may be transmitted by syringes contaminated with the blood of persons harboring the virus⁸³ In an outbreak among 110 men brought about by using one syringe but a different needle for injecting tetanus toxoid in men in batches of 10, symptoms characteristic of acute infectious hepatitis developed fifteen to thirty-eight days afterward in at least 20 per cent of those who could be subsequently studied Blood from unsuspected carriers of the virus evidently got into the syringe and was injected into the others Because of the short incubation period, the infection was classified as infectious hepatitis rather than serum jaundice To account for the epidemic it was estimated that at least 5 per cent of the group must have carried the virus in their blood without showing symptoms The disease in many of those who were infected, because of its mildness and the absence of clinical jaundice, would not have been detected except for the known date of injection, the fact that it was sought for and the evidence of hepatic dysfunction Only 1 patient was clinically jaundiced Four of 10 patients with nonicteric disease were sick

80 Sellers, T F Rabies, the Physician's Dilemma, *Am J Trop Med* **28** 453-456 (May) 1948

81 Johnson, H N Derriengue Vampire Bat Rabies in Mexico, *Am J Hyg* **47** 189-204 (March) 1948

82 Brooksby, J B Vesicular Stomatitis and Foot-and-Mouth Disease Differentiation by Complement-Fixation, *Proc Soc Exper Biol & Med* **67** 254-258 (Feb) 1948

83 Capps, R B, Sborov, V, and Scheffley, C S A Syringe-Transmitted Epidemic of Infectious Hepatitis, *J A M A* **136** 819-824 (March 20) 1948

three months, the condition representing the chronic stage which some believe may lead to cirrhosis

The observations reemphasize the danger of unwittingly transmitting viral hepatitis with blood, syringes and even needles used to prick the skin for blood counts. The possible role of mosquitoes and bedbugs in conveying the virus has not been investigated for want of volunteers

A physician who gave on the average of fifty intravenous injections a day for various reasons to his patients in Italy was imprisoned for the transmission of serum jaundice to at least 100 persons as a result of faulty sterilization of his needles and syringes⁸⁴. Twelve deaths occurred. However, an outbreak of jaundice occurred in another town where the physician had never been, and the incident occurred before Italian physicians were aware of the danger of hematogenous hepatitis

Biopsy of material from the liver by means of aspiration of tissue through an inserted hollow needle is now a recognized method of diagnosis⁸⁵. While harm may occur if the procedure is done carelessly, the danger is minimal. Hemorrhage, puncture of the gallbladder and other accidents may occur and should be anticipated. Two deaths from hemorrhage in sick patients occurred in a series of 150 aspirations⁸⁶. No deaths occurred in the next 250. Details of the method are given in Sherlock's paper⁸⁷.

In Sherlock's and Walshe's cases⁸⁸ of the post hepatitis syndrome, the hepatic tissue in almost all instances was histologically normal. They regard most of the patients as having "hepatic neurosis". In 600 biopsies of material from the liver German investigators⁸⁹ found no evidence of possible development of cirrhosis.

In previous studies, several observers noted the frequent presence of heterophile antibody in the blood of patients with viral hepatitis and falsely positive reactions to Kahn and Wassermann tests. In the studies of Havens and his co-workers⁹⁰ the reaction to the heterophile antibody

84 Epidemic of Homologous Serum Jaundice, Foreign Letters, J A M A 136 209-210 (May 8) 1948. Physicians Imprisoned for the Epidemic of Varese, Foreign Letters, *ibid* 137 1077 (July 17) 1948.

85 Popper, H., and Franklin, M. Diagnosis of Hepatitis by Histologic and Functional Laboratory Methods, J A M A 137 230-234 (May 15) 1948.

86 McMichael, J. Disease of the Liver. A Review of Some Clinical and Biochemical Problems as Revealed by Systematic Biopsy Studies, J A M A 137 234-236 (May 15) 1948.

87 Sherlock, S. P. V. Aspiration Liver Biopsy. Technique and Diagnostic Application, Lancet 2 397-401 (Sept 29) 1945.

88 Sherlock and Walshe, cited by McMichael⁸⁶.

89 Kalk, H., and Buchner, F. Biopic Picture of Epidemic Hepatitis (Laparoscopic and Microscopic Observations), Klin Wchnschr 24-25 878-880 (Nov 15) 1947.

90 Havens, W. P., Gambescia, J. M., and Knowlton, M. Results of Heterophile Antibody Agglutination and Kahn Tests in Patients with Viral Hepatitis, Proc Soc Exper Biol & Med 67 437-440 (April) 1948.

test was positive in only 3 per cent of 508 patients, the reaction to the Kahn test was positive in 15 per cent and the reaction to the cold agglutination test was positive in 2 of 323 patients

"Viral" Dysentery—Several epidemics of this disease are described In Alabama⁹¹ 150 cases were recorded in a community in September and October of 1946 The attack rate in a surveyed group was 40 per cent, the average incubation period three days and the average duration of disease five days All age groups were affected, no likely source of infection was found and attempts to isolate a virus were unsuccessful Enders⁵⁹ reports similar observations and is also trying to discover the cause An outbreak apparently of the same disease occurred in New Haven, and the customary but futile search was made for bacterial contaminants of food and utensils as the cause⁹² The authors evidently did not entertain the newly suggested idea of air-borne viral infection or other means of transmission or indicate that they were aware of them

According to present information, the extensive epidemic in Los Angeles in December, 1947 popularly said to be caused by virus X was apparently caused by three different diseases, influenza A, some undifferentiated mild infection of the respiratory tract and viral dysentery⁹³

Etiology—Gordon and his co-workers⁹⁴ succeeded in transmitting viral dysentery to volunteers by feeding them filtered stools and unfiltered throat washings from patients Inhalation experiments, like the ones my associates and I previously made, were unsuccessful, but volunteers did not inhale fecal filtrates, with which we apparently had success We were unable, on the other hand, to transmit the disease by feeding supposedly infected materials It is still uncertain how the disease is transmitted, but epidemiologic studies⁹⁵ favor the air-borne route in certain outbreaks It is almost certain also that some inhaled material is swallowed It is highly probable, however, that several entities comprise a group of similar diseases, some of which are transmitted orally

91 Smillie, J H , Howitt, B F , and Denison, G A An Epidemic of Acute Watery Diarrhea in Alabama, Pub Health Rep 63 233-243 (Feb 20) 1948

92 Pond, M A , and Hathaway, J S An Epidemic of Mild Gastroenteritis of Unknown Etiology Presumably Spread by Contaminated Eating Utensils, Am J Pub Health 37 1402-1406 (Nov) 1946

93 Perri, A M Epidemic Nausea, Vomiting and Diarrhea, Philadelphia Med 43 1125 (March 20) 1948

94 Gordon, I , Ingraham, H S , and Korns, R F Transmission of Epidemic Gastroenteritis to Human Volunteers by Oral Administration of Fecal Filtrates, J Exper Med 86 409-422 (Nov) 1947

95 (a) Christensen, E , and Biering-Sorensen, K Meningitis- and Encephalitis-like Changes in the Brain of Infants with Severe Gastroenteritis, Acta path et microbiol Scandinav 23 395-406, 1946 (b) Smillie, Howitt and Denison⁹¹ (c) Enders⁵⁹

Our first experiments were made during an epidemic period. To avoid confusion with naturally occurring attacks, further unpublished experiments were made months later in a nonepidemic period with stools preserved at -70°C . The results of the tests were suggestive but again not conclusive. While about 50 per cent of volunteers who inhaled filtrates had characteristic symptoms, similar but milder symptoms occurred in 25 per cent of volunteers who inhaled sterile broth or heated filtrates, as in Topping's experiments on the common cold discussed before. The danger of transmitting poliomyelitis and viral hepatitis through inhalation of feces restricts further experiments of this type.

The commonly used names "epidemic nausea, vomiting and diarrhea" or "gastroenteritis" are unsatisfactory, the first because sporadic cases occur and any one or two of the named symptoms may be absent and the second because there is no evidence of inflammation. There is seldom fever, the leukocytes are normal, there is no blood, pus or mucus in the stools, sigmoidoscopy reveals no more inflammation than would be expected from the diarrhea itself and in cases of similar disease in infants^{95a} no lesions in the intestine were found at necropsy. Even though a virus has not been recovered, there is as much reason to name the disease tentatively viral dysentery as there is for the names viral pneumonia or viral hepatitis. It is hoped that no one will call it "atypical dysentery."

Diarrhea of the Newborn—Necropsy studies by Swedish observers^{95a} revealed no evidence of intestinal infection. There was fatty degeneration of the liver, bronchitis and pneumonia suggestive of a general infection, with gastrointestinal symptoms. They found an encephalitis-like process in 6 instances, meningitis without inflammatory changes in the brain in 18 and edema in 8, but their description of the lesions is unimpressive. The changes may be nonspecific like those of "toxic encephalitis" found in other diseases.

According to Clifford's⁹⁶ review of the literature, epidemic diarrhea in the newborn emerged as a public health problem only after the custom of delivering infants in hospitals instead of at home became prevalent. In many outbreaks apparently caused by a variety of bacteria and in some in which bacteria could not be incriminated, gross defects in nursery technic were discovered, favoring infection by the fecal-oral route. Other outbreaks appear to be caused by viral agents, yet there is no proof for this. There are no methods for reliable diagnostic differentiation. Prevention depends on strict observance of hygienic technic in nurseries and rooms in which formulas are prepared.

96 Clifford, S. H. *Diarrhea of the Newborn Its Causes and Prevention*, New England J. Med. **237** 969-976 (Dec. 25) 1947.

Viral Myocarditis—Schmidt⁹⁷ made further studies on a virus which causes myocarditis in chimpanzees. Passage of the virus in other laboratory animals caused myocarditis and encephalitis. It was thought that the virus may also be the cause of a form of myocarditis in man because the lesions are the same, but there is no evidence of its transmissibility to persons who handle it.

A virus identical with or similar to the one just mentioned is called the virus of encephalomyocarditis and was thought to have caused a mild form of meningitis in American soldiers in Manila. It has a certain relationship to the SK-murine and MM strains of poliomyelitis virus⁹⁸.

Fort Bragg Fever—A virus obtained from patients with this disease, also called pretibial fever, caused fever and viremia and evoked specific neutralizing antibodies in the blood when inoculated into chimpanzees⁹⁹.

Miscellaneous—According to Sprunt,¹⁰⁰ methionine decreased the susceptibility of rabbits to vaccinia but increased the susceptibility of mice to influenza virus especially if the diet was low in protein. Mice on a low protein diet alone are most resistant. No explanation is available to account for the opposite effects of methionine in mice and rabbits.

What is said to be the first example of isolation of a virus from naturally contaminated air is reported. DeLay and his co-workers¹⁰¹ isolated the virus of pneumoencephalitis of poultry, or Newcastle disease, from the air of a poultry house contaminated by sick birds. Burnet once suggested a possible etiologic relationship between Newcastle disease and infectious mononucleosis, but the ability of immune and normal rabbit serums to agglutinate particles of the virus of Newcastle disease seems to be unrelated to the heterophile antibody of mononucleosis or to the hypothetical cause of that disease.¹⁰²

97 Schmidt, E. C. H. Virus Myocarditis. Pathologic and Experimental Studies, *Am J Path* **24** 97-108 (Jan) 1948.

98 Warren, J., and Smadel, J. E. A Serological Relationship Between the Virus of Encephalomyocarditis and Certain Strains of Poliomyelitis-Like Viruses, *Federation Proc* **7** 311-312 (March) 1948.

99 Melnick, J. L., and Paul, J. R. Experimental Fort Bragg Fever (Pretibial Fever) in Chimpanzees, *Proc Soc Exper Biol & Med* **67** 263-269 (March) 1948.

100 Sprunt, D. H. Increased Susceptibility of Mice to Swine Influenza as a Result of Methionine Injections, *Proc Soc Exper Biol & Med* **67** 319-321 (March) 1948.

101 DeLay, P. D., DeOme, K. B., and Bankowski, R. A. Recovery of Pneumoencephalitis (Newcastle) Virus from the Air of Poultry Houses Containing Infected Birds, *Science* **107** 474-475 (May 7) 1948.

102 Evans, A. S., and Curnen, E. C. Serological Studies on Infectious Mononucleosis and Other Conditions with Human Erythrocytes Modified by Newcastle Disease Virus, abstracted, *Federation Proc* **7** 304 (March) 1948.

The electron microscope has been put to practical use in the diagnosis of variola, vaccinia and varicella¹⁰³ Elementary bodies can be demonstrated in the crusts of vesicle fluid Those of varicella are rectangular and uniform, but they are fewer and smaller than those of variola and vaccinia

Studies of Volkert and Horsfall¹⁰⁴ reveal a substance, specific for lung tissue, which has an affinity for PVM (pneumonia virus of mice) and can be neutralized only by specific antibody against the virus The protein complex which occurs is stable except in the presence of specific antibody The observation suggests that the binding of virus is a decisive factor in the initiation of infection Presumably the same may hold for other pneumotropic or other organ-specific viruses Hirst, for example, showed in 1943 that influenza virus is rapidly absorbed by pulmonary epithelial cells, probably by a specific receptor substance

Suspensions of *Shigella alkaescens*, *Hemophilus pertussis* and other bacteria cause clumping of human red cells, as do suspensions of the virus of influenza and of other viruses¹⁰⁵

DISEASES CAUSED BY BACILLI

Tuberculosis—Corper and Cohn¹⁰⁶ again publish pessimistic views on the value of streptomycin for tuberculosis Streptomycin, they write, cannot be considered a cure for tuberculosis since it does not destroy tubercle bacilli or completely retard their growth in culture medium In experiments with animals, streptomycin retarded tuberculosis but did not prevent death therefrom Bogen, who discussed their paper, adds that even if this view is correct the retarding action may be of importance in saving life His animals experimentally infected with tuberculosis often recovered when treated with streptomycin, and in treated patients complete healing of lesions may be observed

In 7 of 8 cases of tuberculosis few resistant tubercle bacilli were present at the beginning of treatment with streptomycin, but in 5 cases there was a gradual increase in their number¹⁰⁷ Oatway¹⁰⁸ considers strepto-

103 Nagler, F P, and Rake, G Use of Electron Microscope in Diagnosis of Varicella, Vaccina and Varicella, *J Bact* **55** 45-60 (Jan) 1948

104 Volkert, M, and Horsfall, F L Studies on a Lung Tissue Component Which Combines with Pneumonia Virus of Mice (P V M), *J Exper Med* **86** 393-407 (Nov) 1947

105 Griffiths, J J Hemagglutination by Bacterial Suspensions with Special Reference to *Shigella Alkaescens*, *Proc Soc Exper Biol & Med* **67** 358-362 (March) 1948

106 Corper, H J, and Cohn, M L Various Phases of the Use of Streptomycin in Tuberculosis, *J A M A* **137** 357-362 (May 22) 1948

107 Pyle, M M Relative Numbers of Resistant Tubercle Bacilli in Sputa of Patients Before and During Treatment with Streptomycin, *Proc Staff Meet, Mayo Clin* **22** 465-473 (Oct 15) 1947

mycin to be a hazard to public health because it engenders streptomycin-resistant tubercle bacilli. Because of the large amounts of streptomycin given for the treatment of tuberculosis and because of its cost, Miller and Rowley¹⁰⁹ recovered 50 to 60 per cent of usable streptomycin from the urine of treated patients by simple adsorption methods. In several instances severe neutropenia has occurred in tuberculous patients while they were taking streptomycin.¹¹⁰

The November and December 1947 issues of the *American Review of Tuberculosis* are almost entirely devoted to articles about the use of streptomycin. Nothing really different from previous views is given. Streptomycin is of value in many forms of tuberculosis, but particularly in tuberculosis of the larynx and trachea. Little or no change occurred in productive or fibrocaseous lesions during one hundred and twenty days of treatment, but evidence of clearing occurred in 85 per cent of exudative lesions. Streptomycin apparently was helpful in the treatment of acute miliary tuberculosis, tuberculous pneumonia and enteritis. Injury to the vestibular apparatus and the development of resistance to the drug by the bacilli were the chief obstacles to therapy.

In one study 36 patients received 3 Gm. of streptomycin intramuscularly daily in divided doses for one hundred and twenty days, others were given 1 Gm. once daily for forty-two days. In the latter group toxic symptoms seldom occurred, but the eventual results of therapy cannot yet be judged. In some patients with early predominantly exudative tuberculosis with recent excavation, the drug caused continuous quiescence, with irregular roentgenologic clearing, but tubercle bacilli persisted in the sputum. In still others symptomatic improvement was variable, excavation continued and the course was progressive, usually accompanied with the appearance of streptomycin-resistant bacilli.

In patients with chronic pulmonary tuberculosis with fibrocavernous changes there was much less improvement, but in 17 of 18 patients some roentgenographic regression of the infiltration was noted. Satisfactory early remission took place in only 4. In 4 patients improvement of a degree sufficient to permit thoracoplasty was attained. In all 43 cases of one series improvement followed streptomycin therapy, but in some the improvement was only slight and transient. Antibiotic therapy can only serve to hold the infection in abeyance in order to give the natural forces of the body a chance to dominate it before too much structural damage

108 Oatway, W. H., Jr. A Streptomycin Hazard to Public Health, Correspondence, J A M A 136 490 (Feb. 14) 1948

109 Miller, J., and Rowley, D. Recovery of Streptomycin from Urine, Lancet 1,404 (March 13) 1948

110 Deyke, V. F., and Wallace, J. B. Development of Aplastic Anemia During the Use of Streptomycin, J A M A 137 599-602 (June 12) 1948

has taken place. Thus far tubercle bacilli were not eradicated from the lungs of even the most successfully treated patients, so that the success of therapy rests on the ability of the patient to control the infection after the use of streptomycin is discontinued. The ideal procedure, barring the danger of toxic symptoms, would be to continue therapy for many months. However, antimicrobial activity usually terminates between the sixtieth and ninetieth days of therapy, when the bacilli almost always became resistant to the drug. It is suggested that patients be treated routinely for forty-two days to avoid development of resistance.

Experiments are now under way to determine whether as little as 0.5 Gm. of streptomycin a day is sufficient.

At present streptomycin therapy is recommended for patients who have progressing, moderately advanced or far advanced pulmonary tuberculosis of recent origin and in whom the disease is predominantly exudative in nature. In cases of chronic disease therapy should be timed in relation to possible surgical operation. Because of its toxicity, streptomycin should not be given to patients with minimal pulmonary tuberculosis or to those with advanced disease in which other methods of therapy are available.

A new class of various benzothiazole derivatives was found to be strongly bacteriostatic for tubercle bacilli and to control tuberculous infection in guinea pigs.¹¹¹ They are of low toxicity.

Because of the reported success in the treatment of leprosy with "promin" (sodium P,P'-diaminodiphenylsulfone—N,N' dioxetose sulfonate), Feldman and his associates¹¹² restudied its effects on experimental tuberculosis. It was found to be effective when given subcutaneously or orally to infected guinea pigs. It is possible that combined therapy with "promin," streptomycin and "promizole" (4,2'-diamino-diphenyl-5'-thiazolesulfone) may be of value in the treatment of tuberculosis.

Concurrent infection in mice caused by *Mycobacterium tuberculosis* and pneumonia virus of mice or influenza virus caused an acceleration of tuberculosis.¹¹³ Presumably the reduction of resistance of the tissues of the respiratory tract by the mild viral infections permitted more rapid

111 Freedlander, B. L., and French, F. A. Chemotherapy of Experimental Tuberculosis with Benzothiazole Derivatives, *Proc. Soc. Exper. Biol. & Med.* **66**: 362-365 (Nov.) 1947.

112 Feldman, W. H., Karlson, A. G., and Hinshaw, H. C. Promin in Experimental Tuberculosis. Antituberculous Effects of Sodium P,P'-Diaminodiphenylsulfone-N,N'-Dioxetose Sulfonate (Promin) Administered Subcutaneously (A Preliminary Report), *Proc. Staff Meet. Mayo Clin.* **23**: 118-123 (March) 1948.

113 Volkert, M., Pierce, C., Horsfall, F. L., Jr., and Dubos, R. J. Enhancing Effect of Concurrent Infection with Pneumotropic Viruses of Pulmonary Tuberculosis in Mice, *J. Exper. Med.* **86**: 203-214 (Sept.) 1947.

development of tuberculosis. In man there is little or no evidence that viral infections cause a similar effect.

Interesting observations were made by Ratchliffe and Wells¹¹⁴ on the course of tuberculosis in rabbits exposed to droplet infection. Up to five weeks all rabbits responded in about the same manner. Tubercle formation began in the second week and progressed to caseation by the fifth week. After this time individual differences appeared and the rate of progress varied, presumably because of different degrees of ability to develop resistance. Animals reinfected within four weeks after the first infection responded like normal ones. The basic effect of acquired resistance of rabbits to tubercle bacilli seems to be bacteriostatic in nature.

BCG Vaccine—Views of the value of BCG vaccine are conflicting. The Norwegians made vaccination legally compulsory for those who are most in danger of contracting tuberculosis.¹¹⁵ Malmros¹¹⁶ in Sweden is enthusiastic about the effects of vaccination. In one vaccinated group of 18,000 only 3 cases of suspected tuberculosis were reported. One fourth of the vaccinated group consisted of newborn babies. Rosenthal¹¹⁷ in Chicago reports 11 cases of tuberculosis in vaccinated babies as compared with 39 cases among controls in a group of 2,800 newborn infants. A positive tuberculin reaction followed vaccination in nearly 93 per cent. Wilson,¹¹⁸ on the other hand, doubts if BCG vaccine has been shown conclusively to have any protective effect at all. If vaccine is used at all, it should, he believes, be restricted to those most exposed to infection, such as nurses or medical students and children in infected households. Vaccine should not be given before the age of 6 months. Wallgren,¹¹⁹ who was largely responsible for the method of vaccination used in Sweden, feels that Wilson's attack on the value of BCG vaccine is in many respects unjust and incorrect. His views are seconded by Malmros.¹²⁰

114 Ratchliffe, H. L., and Wells, W. F. Tuberculosis of Rabbits Induced by Droplet Nuclei Infection. I. Initial Response to Infections, *J. Exper. Med.* **87**: 575-584 (June) 1948; II. Response to Infection, *ibid.* **87**: 585-594 (June) 1948.

115 Compulsory BCG Vaccination, *Foreign Letters*, *J. A. M. A.* **136**: 642 (Feb. 28) 1948.

116 Malmros, H. Late Primary Infection and BCG Vaccination, *Am. Rev. Tuberc.* **56**: 267-278 (Oct.) 1947.

117 Rosenthal, S. R., Leslie, E. I., and Loewensohn, E. BCG Vaccination in All Age Groups, *J. A. M. A.* **136**: 73-79 (Jan. 10) 1948.

118 Wilson, G. S. Value of BCG Vaccination in Control of Tuberculosis, *Brit. M. J.* **2**: 855-858 (Nov. 29) 1947.

119 Wallgren, A. BCG Vaccination. Is It of Any Value in Control of Tuberculosis? *Brit. M. J.* **1**: 1126-1129 (June 12) 1948.

120 Malmros, H. The Efficacy of BCG Vaccination, *Brit. M. J.* **1**: 1129-1132 (June 12) 1948.

Aronson¹²¹ also states the belief that BCG vaccine should be used only for medical students, nurses and hospital personnel and for military personnel in areas with a high tuberculosis rate if such persons give negative reactions to tuberculin BCG as an immunizing agent should serve only as an auxiliary agent with other established methods

At the second national conference on the use of BCG vaccine in New York in March 1948, it was decided that many fundamental problems are yet to be solved¹²² While there is little doubt that BCG is harmless, there is uncertainty as to the degree and duration of immunity it confers Regardless of the ultimate place of BCG, it is unlikely, as in other infectious diseases, that vaccine will ever supersede other control measures Many are of the opinion that in certain localities tuberculosis can be eradicated without vaccine Others fear that vaccination will only confuse the existing epidemiologic pattern by altering the reaction of the skin to tuberculin Therefore, at present there is no justification for relaxing the current methods which are obviously successful

Leprosy—According to McCoy,¹²³ 475 cases of leprosy were reported in California up to 1940, but only 23 persons acquired the disease there, 7 of whom had never been out of the state The majority of patients came from Mexico and the Orient Except for children born of leprosy parents, the danger of the spread of leprosy in California is small McCoy writes that the "incubation period" of leprosy varies between eight and twenty-five years It seems more likely that eight to twenty-five years elapse after infection before clinical symptoms are characteristic enough to permit diagnosis

Up to 1946, 28 cases of leprosy have been recorded among veterans of World War II, of whom 10 came from states in which it is endemic It is predicted that in the future more cases will appear among those who served in military zones in which leprosy exists¹²⁴

What seems to be proof that leprosy can be acquired by infection through the skin was furnished by occurrence of the disease in 2 members of the United States Marine Corps¹²⁵ Both were tattooed by the same artist in Australia, and in both leprosy appeared in the tattooed areas two and one-half years later

121 Aronson, G D The Evaluation of BCG Vaccine in the Control of Tuberculosis, *Tr & Stud, Coll Physicians, Philadelphia* 16 1-13 (April) 1948

122 Weber, F W Further Study of BCG Vaccination, editorial, *Pub Health Rep* 63 593-594 (May 7) 1948

123 McCoy, G W Leprosy in California—Danger of Infection, *Pub Health Rep* 63 705-712 (May 28) 1948

124 Aycock, W L, and Gordon, J E Leprosy in Veterans of American Wars, *Am J M Sc* 214 329-339 (Sept) 1947

125 Porritt, R J, and Olsen, R E Two Simultaneous Cases of Leprosy Developing in Tattoos, *Am J Path* 23-805-818 (Sept) 1947

A "New" Mycobacterial Disease—MacCallum and his co-workers^{125a} describe 6 cases of ulceration of the skin in persons from a district in Australia over a period of several years. Because of the presence of acid-fast bacilli in the lesions, tuberculosis was first suspected, but because of the great numbers of bacilli present, the lack of cellular reaction thereto, their lack of growth on culture mediums used for *M. tuberculosis* and their lack of pathogenicity for guinea pigs, leprosy was considered. This diagnosis was excluded. Because of these peculiarities and of the production of similar lesions in rats and mice by injecting the bacilli, the authors believe that they dealt with a "new" disease. The bacilli are unlike those of any known mycobacterial infection. In speculation on the discovery of a "new" infection questions arise as to whether it is actually new in the sense of never being existent before or arising from variation of bacteria from known forms into new ones, or whether the disease has long existed but is so rare that cases have heretofore been unrecognized.

Brucellosis—Sizable outbreaks of brucellosis are usually caused by *Brucella suis* and *Brucella melitensis*, but in Maryland there were 28 known cases in one caused by *Brucella abortus*.¹²⁶ It was caused by the addition of raw milk from an infected herd to supplement an inadequate supply of "clean" milk.

Three groups of observers¹²⁷ favor the combined use of streptomycin and sulfadiazine for treatment. In Spink's^{127c} series recovery was recorded as complete in 5 and apparently complete in 3 of 9 patients so treated, including some with endocarditis and spondylitis. In Eisele's^{127b} cases brucellas persisted in blood which contained two to five times the amount of streptomycin needed to kill them in the test tube. Bacilli were still present after treatment was stopped, which makes one skeptical of its curative effect. Success with combined drugs in a case of chronic brucellosis is reported.¹²⁸ Numerous speakers at an inter-American Congress on brucellosis in Argentina in November 1948 described disappointing results. Combined therapy was also ineffective for infections with *Br*

125a MacCallum, P., and others. A New Mycobacterial Infection in Man, *J. Path. & Bact.* **60** 93-122 (Jan.) 1948.

126 Steele, J. H., and Hastings, J. W. Report of Brucellosis Outbreak at Federalsburg, Maryland, *Pub. Health Rep.* **63** 144-145 (Jan. 30) 1948.

127 (a) Pulaski, E. J., and Amspacher, W. H. Streptomycin Therapy in Brucellosis, *Bull. U. S. Army M. Dept.* **7** 221-226 (Feb.) 1947. (b) Eisele, C. W., and McCullough, N. B. Combined Streptomycin and Sulfadiazine Treatment in Brucellosis, *J. A. M. A.* **135** 1053-1055 (Dec. 20) 1947. (c) Spink, W. W., Hall, W. H., Shaffer, J. M., and Brande, A. I. Human Brucellosis. Its Specific Treatment with a Combination of Streptomycin and Sulfadiazine, *ibid.* **136** 382-387 (Feb. 7) 1948.

128 Harris, H. J., and Jett, P. C. Streptomycin and Sulfadiazine (Combined) in Chronic Brucellosis, *J. A. M. A.* **137** 363-364 (May 22) 1948.

melitensis ^{128a} Aureomycin is now said to be the most effective agent, but in treatment of 24 patients several relapses occurred ^{128a}

Vaccination with the customary heat-killed *Brucella* and treatment with various drugs gave disappointing results in therapy, but supposed desensitization with ultramminute fractionated dosage of an "oxidized brucella vaccine" before larger amounts were given was said to be effective ¹²⁹ The authors report studies of 300 cases of chronic brucellosis over a ten year period If one physician can collect so many cases of an uncommon disease, it must be that the rest overlook it frequently or that all his cases were not those of chronic brucellosis

Since a common antigenic relationship apparently exists between the *Brucella* organism and *Vibrio comma*, vaccination against cholera may evoke agglutinin which clumps the *Brucella* ¹³⁰ As a result, diagnostic confusion, especially with chronic brucellosis, is likely to be encountered until the agglutinin vanishes in some of the 3,000,000 veterans who have been vaccinated against cholera Over half of 100 persons who had received cholera vaccine had an agglutinin titer for brucella of 1/20 or higher, and in 20 per cent the titer was over 1/80 Agglutinin may persist for twenty-eight months ¹³¹

Two cases of brucellosis, 1 of them doubtful, are reported in which there were chronic diffuse pulmonary changes ¹³²

Diphtheria—The diphtheria pandemic in Europe during the war led to an extensive study of the subject in Denmark ¹³³ Between October 1943 and April 1944, 403 cases were observed The group involved was different from that in earlier years in that 70 per cent of patients had been immunized Of 403 patients, 36 died, and none of these had been immunized previously Of 54 strains of diphtheria bacilli recovered during the study, 37 were of the gravis type, 16 of the mitis type and 1 of the intermedius type The importance or validity of such classification is questioned by many Electrocardiographic changes were present in 85 per cent of the cases arbitrarily classified as severe At necropsy diphtheria

128a Spink, W W , Braude, A I , Casteneda, M R , and Goytia, R S Aureomycin Therapy in Human Brucellosis Due to *Brucella Melitensis*, J A M A **138** 1145-1148 (Dec 18) 1948

129 Griggs, J F Chronic Brucellosis Conclusions on Treatment After Ten Years, J A M A **136** 911-915 (April) 1948

130 Eisele, C W , McCullough, N B , Beal, G A , and Rottschaefer, W *Brucella* Agglutination Tests and Vaccination Against Cholera, J A M A **135** 983-984 (Dec 13) 1947

131 Eisele, C W , McCullough, N B , and Beal, G A *Brucella* Antibodies Following Cholera Vaccination, Ann Int Med **28** 833-837 (April) 1948

132 Harvey, W A Pulmonary Brucellosis, Ann Int Med **28** 768-781 (April) 1948

133 Ammundsen, E , and others Types of Diphtheria Bacillus and Clinical Diphtheria, Acta med Scandinav **129** 415-440, 1948

bacilli were found in the lungs in 65 per cent, in the blood in 13 per cent, in the spleen in 8 per cent and in the liver in 5 per cent of patients. Hemolytic streptococci were found in practically the same percentages and were thought to contribute to the severity of the disease.

In an epidemic of diphtheria in Utah in 1947 there were 117 known cases and 11 deaths.¹³⁴ The mitis strain of diphtheria bacilli was isolated from 74 per cent of patients, the minimus from 18 per cent and the gravis from 6 per cent. Thirty per cent of patients had been previously immunized against diphtheria. No deaths occurred in those from whom the minimus strain was isolated.

Tularemia —Bost and his associates¹³⁵ report on 54 cases of tularemia in the Ozark region, in 27 of which streptomycin therapy was applied. The results were striking. In the untreated patients the average duration of disease was fourteen days, but in those treated it was one day after therapy. Three untreated patients died, and all treated ones, including several with pneumonia, recovered. According to Foshay,¹³⁶ the administration of a total dose of 2 or 3 Gm. of streptomycin is usually enough, more is wasteful.

Plague —Primary pneumonic plague recurred in Mukden in February 1946 for the first time since 1921.¹³⁷ It was thought to have been brought in by a carrier, but the infection probably resided there in rats endemically. The incubation period seemed to be three to five days. Three patients treated with sulfadiazine early in the course recovered. Four of 42 persons who had contact with patients harbored *Pasteurella pestis* in their throat for six to fifteen days without becoming sick. Sulfonamide therapy has also reduced the death rate in Brazil.¹³⁸

Pneumonic plague appeared in September 1946 in Rangoon, where plague is endemic.¹³⁹ The first 10 cases were unrecognized, as often happens. The outbreak affected a crowded community grouped about a small factory. Although pneumonic plague is usually regarded as extremely contagious and has been mentioned as a likely agent for bacterial war-

134 Jenkins, A. A. Diphtheria Epidemic in Utah in 1947, *Pub Health Rep* **63** 573-577 (April 30) 1948. Galbraith, T. W. Appearance of "Minimus" Type Diphtheria in Utah, *ibid* **63** 577-579 (April 30) 1948.

135 Bost, R. B., Percefull, S. C., and Leming, H. E. Tularemia in the Ozarks Region, *J A M A* **137** 352-354 (May 22) 1948.

136 Foshay, L. Streptomycin in Treatment of Tularemia, *J Indiana M A* **41** 207-210 (Feb.) 1948.

137 Tieh, T. H., Landauer, E., Miyagawa, F., Kobayaschi, I., and Okayasu, G. Primary Pneumonic Plague in Mukden 1946, and Report of Thirty-Nine Cases with Three Recoveries, *J Infect Dis* **82** 52-58 (Jan-Feb.) 1948.

138 Plague in Brazil, *Foreign Letters*, *J A M A* **136** 710 (March 6) 1948.

139 Wynne-Griffith, G. Pneumonic Plague in Rangoon, *Lancet* **1** 625-627 (April 24) 1948.

fare, events in the present outbreak suggested otherwise. Examples of close and prolonged contact with patients without contagion are cited which leads to the statement that "generally the disease is not particularly infectious." Numerous other reported examples of low infectivity are quoted. The fact that many of the observations were made in hot climates may account for the low contagiousness. Pneumonic plague is thought to spread with more ease in cold weather, but this may not be so. Contagion may be enhanced by concomitant minor viral infections of the respiratory tract, more common in winter, which prepare the tissue for easier invasion.

A similar circumstance is reported by Huang and his associates¹⁴⁰ in Nanking. Pneumonic plague developed in a laboratory technician while he was working with plague bacilli. Of 15 persons who had close contact with him during the disease, none contracted the infection. All contacts, however, received 3 to 6 Gm of sulfadiazine daily for one week as a prophylactic measure. It is uncertain how much credit can be given to its effectiveness. The patient was given 21 Gm of streptomycin over eighteen days, during which time the fever tended to fall. It ended abruptly on the eighteenth day. Sulfadiazine was also given. The plague bacilli, sensitive to streptomycin at first, became resistant to 200 mg per hundred cubic centimeters.

Streptomycin was highly effective in controlling both septicemic and pneumonic plague in experimentally infected mice, even when given late in the course of the disease.¹⁴¹ On a proportionate basis, 2 to 4 Gm daily is recommended for plague in human beings. Streptomycin used in India¹⁴² gave good results within thirty-six hours.

Tetanus—Tetanus toxoid as employed by the Naval Medical Services was highly effective in preventing the disease.¹⁴³ Active immunization with this is superior to passive immunization with antitoxin. Both plain and alum-precipitated toxoids are effective, the latter being preferred. Four cases of tetanus occurred during the war, the 2 victims who recovered had received the usual immunizing treatment, and the 2 who died had not.

Reference was made previously to an epidemic of viral jaundice inadvertently induced during immunization with the use of contaminated syringes.

140 Huang, C H , Huang, C Y , Chu, L W , and Huang, T F. Pneumonic Plague. A Report of Recovery in a Proved Case and a Note on Sulfadiazine Prophylaxis, *Am J Trop Med* 28 361-371 (May) 1948.

141 Quan, S F , Foster, L E , Larson, A , and Meyer, K F. Streptomycin in Experimental Plague, *Proc Soc Exper Biol & Med* 66 528-532 (Dec) 1947.

142 Karamchandani, P V , and Sundar Rao, K. Streptomycin in Human Plague, *Lancet* 1 22 (Jan 3) 1948.

143 Hall, W W. The U S Navy's War Record with Tetanus Toxoid, *Ann Int Med* 28 298-308 (Feb) 1948.

Anthrax—Anthrax in a wool picker was treated with penicillin and antianthrax serum¹⁴⁴ During treatment, meningitis was suspected, the spinal fluid was normal, but anthrax bacilli were cultivated therefrom Penicillin was then given intrathecally and sulfadiazine orally The spinal fluid soon became cloudy with cells Intrathecal therapy may have brought about recovery, but it may have been unnecessary and it probably caused "sterile meningitis"

Anthrax affects elephants Caretakers¹⁴⁵ and handlers of raw ivory¹⁴⁶ have contracted the disease

Rhinoscleroma—A patient who had had rhinoscleroma for fifteen years was apparently cured with streptomycin¹⁴⁷ Bacilli of the *Klebsiella* group thought to be the cause of the condition were present and disappeared after therapy

ENTERIC DISEASES

After Boivin's and Poe's success in causing type transformation of colon bacilli, Weil and Binder¹⁴⁸ succeeded in changing Flexner dysentery bacilli from one type into another by growth in filtrates of the type strain into which the bacillus was changed The instability of supposedly fixed types of bacteria is thus becoming more and more evident, raising the whole question of classification and type specificity As regards dysentery bacilli, instability may account for the great variety of listed strains It may also explain the lack of success in devising measures for specific immune prophylaxis and therapy

Studies along similar lines¹⁴⁹ on *Salmonella* show that strains of bacilli of this group of bacilli also may transform themselves into another type In the experiments a strain of *Salmonella* simsbury, by growth in specific serum of *Salmonella* senftenberg, was induced to change into the latter variety Bacilli of the senftenberg type were then grown in other anti-

144 Shanahan, R H , Griffin, J R , and Auersperg, A P Anthrax Meningitis Report of a Case of Internal Anthrax with Recovery, *Am J Clin Path* **17** 719-721 (Sept) 1947

145 Anthrax in Elephants, Queries and Minor Notes, *J A M A* **135** 1042 (Dec 13) 1947

146 Seideman, R M , and Whaler, K M Elephant Tusks A Source of Human Anthrax, *J A M A* **135** 837-838 (Nov 29) 1947

147 Devine, K D , Weed, L A , Nichols, D R , and New, G B Rhinoscleroma Apparently Cured with Streptomycin, *Proc Staff Meet, Mayo Clin* **22** 597-600 (Dec 24) 1947

148 Weil, A J , and Binder, M Experimental Type Transformation of *Shigella* *Paradysenteriae* (Flexner), *Proc Soc Exper Biol & Med* **66** 349-352 (Nov) 1947

149 Edwards, P R , Moran, A B , and Bruner, D W Intertransformability of *Salmonella* *Simsbury* and *Salmonella* *Senftenberg*, *Proc Soc Exper Biol & Med* **66** 230-232 (Oct) 1947

serum, which induced the appearance of still another type which when once more cultivated in homologous serum caused reversion to bacilli of the original simsbury form. By replacement of the eponyms with the improved nomenclature indicating fixed O and H antigens, the schematic behavior of the transformations appears as follows: I, III, XIX $Z_{27} \rightarrow$ I, III, XIX $g s t \rightarrow$ I, III, XIX $Z_{34} \rightarrow$ I, III, XIX Z_{27} . The new scheme of classification looks complicated, but it really simplifies matters. It shows further how unstable bacilli may be and that supposed "new" types may only be variant forms of each other. Similar phenomena are known to occur with pneumococci and *Micrococcus tetragenus*.

Studies by Hardy and his co-workers¹⁵⁰ support other recent work regarding the uselessness of vaccines given parenterally for the prevention of shigellosis.

Hardy and Halbert gave streptomycin orally to 37 patients with bacillary dysentery.¹⁵¹ Some received 3 Gm and some 6 Gm in four divided doses daily. Others were given 4 Gm of sulfadiazine daily. *Shigellas* decreased rapidly in the stools after streptomycin therapy and were absent after the sixth day, but by the fourteenth day six stools again contained dysentery bacilli. After sulfadiazine therapy all stools were free from dysentery bacilli by the third day, and there were no recurrences. Streptomycin therefore appears to be of value when *Shigella* are resistant to sulfonamide compounds. Its use is also desirable if the patient is sensitive to the latter.

In efforts¹⁵² to detect the source of outbreaks of food poisoning, the presence of *Streptococcus fecalis* in suspected food is often disregarded because it has little, if any, virulence and is a common inhabitant of human feces. Nevertheless, these cocci were implicated as possible causes of four outbreaks of food poisoning acquired by eating milk products or meats. Volunteers were fed five hour cultures of *Str. fecalis*, but in only 6 of 26 did suggestive symptoms of "food poisoning" follow.¹⁵³

A somewhat similar opinion¹⁵⁴ incriminates paracolon bacilli as causes in certain instances of chronic dysentery. These bacilli commonly

150 Hardy, A. V., DeCapito, T., and Halbert, S. P. Studies of the Acute Diarrheal Diseases. XIV Immunization in Shigellosis, *Pub Health Rep* **63** 685-688 (May 21) 1948.

151 Hardy, A. V., and Halbert, S. P. XX Further Observations of Chemotherapy in Shigellosis. The Efficacy of Streptomycin and Sulfacarazole, *Pub Health Rep* **63** 790-792 (June 11) 1948.

152 Buchbinder, L., and Steffen, G. I. Studies in Enterococcal Food Poisoning, *Pub Health Rep* **63** 109-118 (Jan 23) 1948.

153 Osler, A. G., Buchbinder, L., and Steffen, G. I. Experimental Enterococcal Food Poisoning in Man, *Proc Soc Exper Biol & Med* **67** 456-459 (April) 1948.

154 Darnall, C. R. Paracolon Bacilli as Related to Chronic Dysentery Syndromes, *Gastroenterology* **10** 366-376 (March) 1948.

found in the intestine are not regarded as pathogens, but evidence in several cases described strongly suggests that they are pathogenic. Streptomycin given orally and parenterally eliminated paracolon bacilli in 5 patients, and clinical improvement followed. Analysis of strains of paracolon bacilli revealed that 70 per cent of them contained antigens common to *Salmonella* or *Shigella*.

Typhoid—German¹⁵⁵ and Chinese¹⁵⁶ observers regard aspiration and culture of the marrow as the best method to obtain typhoid bacilli from patients.

After a comprehensive review of the subject, Dolman¹⁵⁷ concludes that there is no justification for vaccination against enteric infections by the oral route.

Mention was previously made of the effectiveness of chloromycetin in the treatment of typhoid.

Cholera—Cholera in epidemic form appeared in Syria, Lebanon and Egypt¹⁵⁸ in the late fall of 1947. According to a brief report on the Egyptian outbreak, which lasted about eight weeks, over 20,000 cases and 10,000 deaths occurred, a mortality rate of 50 per cent. In the last epidemic in 1902 the rate was said to have been 85 per cent. It is unlikely that the rate is even as high as the lesser figure given. Many observers diagnose cholera only if the patient is extremely sick or dies, mild attacks are usually ignored or regarded as some other form of enteritis. As usual, and most likely wrongly, vaccine is given much credit for controlling the outbreak, but it is admitted that the decline may have been spontaneous.

Cholera was erratically distributed in the Egyptian outbreak. Seldom was more than one member of a household attacked. The victims were generally either parasite ridden or senile, or they had pellagra, malaria or other disease or were young children. Achlorhydria, presumably a factor enabling vibrios to survive in the stomach, is commonly found in debilitating conditions. Alkalinity in the intestine also favors the growth of vibrios.¹⁵⁹

155 Rogge, K. Value of Bone Marrow Puncture as Diagnostic Aid in Children with Typhoid, *Arch f Kinderh* **134** 1-5 (June) 1947.

156 Ling, C. C., Liu, J., and Chen, T. Y. A Comparative Study of Bile, Marrow, Blood, Stool, Urine Cultures and Widal Reaction in Typhoid and Paratyphoid Fevers, *Chinese M J* **66** 66-78 (Feb.) 1948.

157 Dolman, C. E. Oral Immunization, *Am J M Sc* **215** 327-351 (March) 1948.

158 Cholera in Syria and Lebanon, *Foreign News*, *JAMA* **136** 195 (Jan 17) Report on Cholera in Egypt, *General News*, *ibid* **136** 196, 1948.

159 Abdou, S. Susceptibility to Cholera, *Lancet* **1** 903-904 (June 12) 1948.

Because Bhatnagar¹⁶⁰ in India found that hexamethylenetetramine killed the cholera vibrio and because of the reported success of sulfonamide compounds in treatment, a new compound of sulfathiazole and formaldehyde was tested. Eighty-five patients were treated with the new drug, called "6257." The average amounts given over several days to children was 16 Gm and to adults 23 to 30 Gm orally. A large initial dose of 6 Gm was given. The effects were much better than those after the use of the usual sulfonamide drugs. Distinct improvement was said to occur at the end of twenty-four hours. Apparently no fluid was injected parenterally. Almost all treated patients survived. The mortality rate among untreated patients in the same outbreak is not stated. The drug is said to be of value in prophylaxis during the theoretic "negative" phase after vaccination and to prevent the spread of infection to others. Vibriones were said to be absent from stools of treated patients. If the value of this compound is confirmed elsewhere, it will be a great boon. It will permit the treatment of hundreds of patients in an outbreak and obviate the cumbersome but effective method of parenteral rehydration.

In experimental studies, Burrows and his associates¹⁶¹ were able to induce actual infection and multiplication of vibrios in the intestine of guinea pigs fed with the germs after the manner used by Koch. The infection is truly an enteric one confined to the lumen of the intestine. In guinea pigs which had been infected previously or immunized with vaccine the number of excreted vibrios was greatly reduced and the duration of infection lessened. Specific antibody (coproantibody) appeared early in the feces, was associated with serum globulin and apparently was excreted or secreted into the intestinal lumen from the blood. Antibodies appeared more slowly in the blood but persisted much longer than those in the feces.

A substance in filtrates of cultures of the cholera vibrio has a destructive specific action on the epithelium of the guinea pig's ileum.¹⁶² It is not in autolysates of vibrios, but it is a somatic antigen and evokes neutralizing antibodies.

MENINGITIS

Meningitis Caused by Meningococci and H. Influenzae—In separate papers dealing with meningitis caused by meningococci and

160 Bhatnagar, S. S., de Sa, J., Fernandes, F., and Divekar, P. V. Chemotherapy of Cholera with a New Sulphonamide Compound ("6257"). Laboratory Investigation and Field Trials, Brit. M. J. 1 719-723 (April 17) 1948.

161 Burrows, W., Elliott, M. E., and Havens, I. Studies on Immunity to Asiatic Cholera. IV. Excretion of Coproantibody in Experimental Enteric Cholera in the Guinea Pig, J. Infect. Dis. 81 260-281 (Nov-Dec) 1947.

162 Wei, S. H., and Hao, S. H. Immunological Studies of Cholera Filtrates, Federation Proc. 7 310 (March) 1948.

H. influenzae, Hoyne¹⁶³ reemphasizes the importance of doing as few spinal punctures as possible and avoiding intrathecal therapy. This alone, he believes, has contributed much to the improved mortality rate of the disease. Aside from an initial spinal puncture for diagnosis, 97 per cent of his patients were treated without intrathecal therapy or drainage of spinal fluid. Even the initial puncture was not always needed for diagnosis if cultures of the blood or of the dermal lesions revealed meningococci. With the exclusion of moribund patients admitted to the hospital, the mortality rate among 660 patients was 6 per cent! In a much smaller number of cases my experience has been similar. Hoyne and Brown treat their patients with sulfonamide drugs, preferably sulfathiazole, giving the first dose intravenously and the rest orally when possible. The level of the sulfonamide drug attained in the blood is of no great importance when the average dosage is given, and the amount entering the spinal fluid is said not to be a determining factor in recovery, a view with which I agree. Hoyne does not favor the use of penicillin for meningococcic meningitis.

For meningitis caused by *H. influenzae*, Hoyne and Brown regard intrathecal therapy as "totally unnecessary," nor is type-specific antiserum needed when the dosage of streptomycin and sulfadiazine is adequate. These are opinions with which I also concur. Of their 28 patients, 26 recovered after oral and parenteral therapy with a sulfonamide compound and streptomycin.

Gonococcic Meningitis—A case of gonococcic meningitis ostensibly resulting from chronic prostatitis caused by a urethral infection fifteen years previously is reported.¹⁶⁴ While it is reasonable that this sequence of events occurred, the matter of differentiating gonococci from meningococci and related or similar gram-negative cocci is not easy. The criteria used for the recognition of the cocci as gonococci were the colonial characteristics on chocolate agar, fermentation of dextrose and a change of color from pink to black with dimethyl-para-phenylenediamine hydrochloride.

Tuberculous Meningitis—Lincoln and her co-workers¹⁶⁵ treated 7 patients with tuberculous meningitis with 'promizole' (4,2'-diamino-

163 Hoyne, A. L. and Brown, R. H. Seven Hundred and Twenty-Seven Cases. An Analysis, *Ann Int Med* 28:248-259 (Feb.) 1948. (a) Intrathecal Therapy Not Required for *H. Influenzae* Meningitis. A Report of Twenty-Eight Cases, *J A M A* 136:597-601 (Feb. 28) 1948.

164 Stigler, S. L., and McLester, J. S. Gonococcic Meningitis Fifteen Years After Urethritis, *J A M A* 136:919-920 (April 3) 1948.

165 Lincoln, E. M.; Kirmse, T. W., and DeVito, E. Tuberculous Meningitis in Children. A Preliminary Report of Its Treatment with Streptomycin and Promizole, *J A M A* 136:593-597 (Feb. 28) 1948.

phenyl-5'-thiazolesulfone) combined with a streptomycin, the former was given orally and the latter intramuscularly and intrathecally. The combination was given because streptomycin acts quickly but is toxic and the effects of "promizole" are usually delayed for several weeks and it is less toxic. Of their 7 patients, 6 no longer have evidence of neurologic disorder and are normal mentally.

STREPTOCOCCI

Varying results are reported of the effectiveness of penicillin in ridding carriers of hemolytic streptococci.¹⁶⁶ Success was attained in 18 of 20 patients by giving 1,200,000 units of penicillin over ten days. Others¹⁶⁷ using 100,000 units a day found that the incidence of beta hemolytic streptococci remained the same as in the control group without treatment. Streptococci resistant to more than 10 units of penicillin were then found in 82 per cent of treated patients and in 40 per cent of the control group. Those in the control group were probably acquired by contact with persons of the treated group. When larger doses were given, 1,000,000 units a day, hemolytic streptococci usually disappeared. The use of penicillin as a prophylactic agent is suggested to prevent infection by beta hemolytic streptococci which may induce rheumatic fever.

There is no evidence as yet of the development of resistance to penicillin among pathogenic strains of hemolytic streptococci, pneumococci or gonococci in patients during the course of therapy.¹⁶⁸ Hemolytic streptococci may become somewhat resistant during growth in penicillin-containing medium in cultural tests, but the resistance is temporary.

In three papers in the *Proceedings of the Society of Experimental Biology and Medicine* of February, Gezon reports the acquisition of a seventeenfold resistance on the part of some strains of group A hemolytic streptococci by growth in mediums containing penicillin. Other strains increased resistance sixfold after sixty subcultures. Resistant strains lost much invasiveness. The resistance disappeared after subculture in penicillin-free medium.

166 Goerner, J. R., Massell, B. F., and Jones, T. D. Use of Penicillin in Treatment of Carriers of Beta-Hemolytic Streptococci Among Patients with Rheumatic Fever, *New England J. Med.* **237**: 576-579 (Oct. 16) 1947.

167 Milzer, A., Kohn, K. H., and MacLean, H. Oral Prophylaxis of Rheumatic Fever with Penicillin. Resistant Hemolytic Streptococci, *J. A. M. A.* **136**: 536-538 (Feb. 21) 1948.

168 Weinstein, L., and Tsao, C. C. L. In Vitro Development of Temporary Penicillin-Resistance in *Streptococcus Pyogenes*, *Proc. Soc. Exper. Biol. & Med.* **66**: 598-602 (Dec.) 1948. Hartman, T. L., and Weinstein, L. Drug Sensitivity of Hemolytic Streptococci Isolated from Cases of Scarlet Fever Treated with Penicillin, *ibid.* **69**: 314-316 (Nov.) 1948.

Rothbard and Watson¹⁶⁹ show that during the course of disease caused by group A hemolytic streptococci certain variation takes place in the bacteria. There is a gradual decrease in the amount of the type-specific M protein, which subjects them to greater bacteriostatic action by the blood. These avirulent variants could be caused to revert to the original form by passage in mice. From previous work on the pneumococcus, I suspected that a change from virulence to avirulence involving the M→S→R phase transformation played a role in recovery from infection, but I was unable to demonstrate it.

Rheumatic Fever—In place of sulfadiazine as a prophylactic agent against hemolytic streptococcus infection of the respiratory tract as a measure to prevent recurrences of rheumatic fever, 500,000 units of penicillin was given in troches after each meal to 22 children observed in a cardiac clinic.¹⁷⁰ None had signs of rheumatic activity, in contrast with the occurrence in a similar but untreated group of children, in 4 of whom such signs developed.

In a long, discursive paper reviewing the nature of viruses in general, Gordon¹⁷¹ resurrects the controversy on whether a virus is the cause of rheumatic fever. He feels that it is improbable that the streptococcus is more than an associated agent, but it is the commonest of all invaders whatever the primary cause may be. Because certain cellular reactions in cases of Hodgkin's disease and of rheumatic fever resemble the histologic changes caused by certain viruses, the author believes both to be caused by viruses. The conclusion is written: "The chief infective agent in rheumatic fever, the rheumatic granuloma of Aschoff, is almost certainly a virus."

McKeown¹⁷² reopens the other long-standing problem of the possible allergic nature of acute rheumatic fever. Lesions which resemble those of rheumatic fever were evoked in the cardiovascular system by sensitizing rabbits with horse serum and reinjecting horse serum later. Similar results were reported after the use of egg albumin.¹⁷³

Arthritis—A comprehensive review of the literature on rheumatism and arthritis by Hench¹⁷⁴ and his collaborators includes papers pub-

169 Rothbard, S., and Watson, R. F. Variation Occurring in Group A Streptococci During Human Infection, *J. Exper. Med.* **87** 521-533 (June) 1948.

170 Maliner, M. M., and Amsterdam, S. D. Oral Penicillin in the Prophylaxis of Recurrent Rheumatic Fever, *J. Pediat.* **31** 658-661 (Dec.) 1947.

171 Gordon, M. Is Rheumatism a Virus Disease? *Lancet* **1** 697-701 (May 8) 740-744 (May 15) 1948.

172 McKeown, E. T. Experimental Serum Carditis and Its Relationship to Rheumatic Fever, *J. Path. & Bact.* **59** 547-555 (Oct.) 1947.

173 Moore, F. G., and others. Production of Acute Rheumatic-Like Heart Lesions in Mice, *Proc. Soc. Exper. Biol. & Med.* **65** 102-107 (May) 1947.

lished between 1941 and 1945 Over two thousand references are listed

According to Rose and his co-workers,¹⁷⁵ the serum of patients with active rheumatoid arthritis, but not that from patients with other conditions, causes agglutination of sensitized sheep erythrocytes in titers several fold higher than agglutination of normal sheep erythrocytes Since this reaction seems to be unique for rheumatoid arthritis, it may serve as an aid in differential diagnosis and to determine the degree of activity The reaction is unrelated to other known ones

Two authors¹⁷⁶ treated patients with arthritis by hot fomentations for seventy-two hours, followed by Speransky's barbarous "spinal pumping," six fever sessions induced by killed typhoid bacilli, autohemotherapy, nicotinic acid and physical therapy Fortunately for the patients, they seem to have escaped vaccine therapy, chrysotherapy, prostigmine, bee venom injections, loss of teeth, tonsils or other detachable organs and further futile gestures¹

DISEASES CAUSED BY FUNGI

Coccidioidomycosis—Groover and his associates¹⁷⁷ studied 1,220 soldiers with asymptomatic pulmonary pathema, discovered on roentgenographic examination Of these, the sputum of 50 per cent contained no tubercle bacilli, and 3.5 per cent reacted negatively to the tuberculin skin test All were considered to have tuberculosis unless it was proved otherwise Cutaneous tests were made with tuberculin, coccidioidin and histoplasmin About 97 per cent were sensitive to tuberculin, 59 per cent to histoplasmin and 31 per cent to coccidioidin Many reacted to all three antigens Three patients reacting to coccidioidin and tuberculin had both acid-fast bacilli and spherules of *Coccidioides* in their bronchial secretions *Histoplasma capsulatum* was not found in any The incidence of pulmonary calcifications was greater in persons sensitive to histoplasmin Obviously the use of the skin test for histoplasmosis was of limited value in differential diagnosis and the present methods used for the differential diagnosis of pulmonary infections are inadequate In 4 former soldiers who had served in endemic areas coccidioidomycosis developed after they

174 Hench, P. S., and others. Rheumatism and Arthritis. Review of American and English Literature of Recent Years, (Ninth Rheumatism Review), *Ann Int Med* **28** 66-168 (Jan), 309-451 (Feb) 1948

175 Rose, H. M., Ragon, C., Pearce, E., and Lipman, M. O. Differential Agglutination of Normal and Sensitized Sheep Erythrocytes by Sera of Patients with Rheumatoid Arthritis, *Proc Soc Exper Biol & Med* **68** 1-6 (May) 1948

176 Boucek, R. J., and Lowman, E. W. Vascular Approach to the Treatment of Rheumatoid Arthritis, *Am J M Sc* **215** 198-208 (Feb) 1948

177 Groover, M. E., and others. Sensitivity of Skin to Histoplasmin in Differential Diagnosis of Pulmonary Disease, *Arch Int Med* **80** 496-573 (Oct) 1947

returned to their homes in New England¹⁷⁸ Each had evidence of mild pulmonary involvement The report again emphasizes that the disease must be suspected in areas in which it is not endemic when puzzling lesions of the skin or pulmonary involvement develops in patients who have been in endemic regions

Smith¹⁷⁹ reports a case of coccidioidomycosis in a dog in Iowa The animal had been in Texas a year before and may have been infected there However, coccidioidomycosis has been observed as far as the states bordering Iowa to the west and south Coccidioidal granuloma has been recorded in cattle and sheep

Histoplasmosis—It is evident that most persons infected with *H capsulatum* do not have grave or fatal disease As with coccidioidomycosis, the majority of cases are mild and have been heretofore unrecognized Stuart and his associates¹⁸⁰ studied a first observed case in which there was recovery from a moderately severe attack The acute phase of the disease resembled viral pneumonia with pleural effusion and lasted about a month, but low grade fever persisted for three months Diagnosis was made from a positive reaction to a histoplasmin test, the finding of the typical bodies in circulating mononuclear cells and the cultivation of the fungus from the pleural exudate

An analogy between histoplasmosis and coccidioidomycosis is becoming more and more evident Both were once thought to be fatal diseases until the majority of cases were found to be mild The causative fungi are found in rodents¹⁸¹ and dogs,¹⁷⁹ but while *Coccidioides immitis* has been found outside the animal body, *H capsulatum* has not It probably will be eventually The fact that the disease is most prevalent in the mid-western states suggests that conditions there are favorable to its growth and spread There is some question of the specificity of the histoplasmin skin test in the diagnosis of mild cases, particularly in the Middle West, or of previous attacks of the disease, but the greater number of severe cases in the same region seems to verify its value in case finding In that region pulmonary infiltrations and calcifications are most often the result of histoplasmosis¹⁸²

178 Kurz, E R H, and Loud, N W Coccidioidomycosis in New England, New England J Med **237** 610-616 (Oct 23) 1947

179 Smith, H Coccidioidomycosis in Animals with Report of a New Case in a Dog, Am J Path **24** 223-230 (Jan) 1948

180 Stuart, B M, Gardner, J W, LeMone, D V, and Van Ravenswaay, A C Pulmonary Histoplasmosis, J Missouri M A **45** 417-421 (June) 1948

181 Emmons, C W, Bell, J A, and Olson, B J Naturally Occurring Histoplasmosis in *Mus Musculus* and *Rattus Norvegicus*, Pub Health Rep **62** 1642-1646 (Nov 14) 1947

182 Furcolow, M I, Mantz, H L, and Lewis, I The Roentgenographic Appearance of Persistent Pulmonary Infiltrates Associated with Sensitivity to Histoplasmin, Pub Health Rep **62** 1711-1718 (Dec 5) 1947

A complement fixation test has been devised for the diagnosis of histoplasmosis¹⁸³ Of 300 serums, 14 reacted positively, of which 9 came from patients with histoplasmosis The most efficient medium for the isolation of *H capsulatum* is brain-heart infusion blood agar incubated at room temperature

Now that diagnostic methods are available, the diagnosis will be made in more instances, and this undoubtedly will lead to the erroneous idea that the disease is spreading For example, since 1944, 9 cases have been recognized as far east as Pennsylvania, most of them severe¹⁸⁴ From the 100 cases now on record, it is evident that the disease as a primary infection is not so difficult to recognize as when it accompanies other serious conditions such as Hodgkin's disease, sarcoidosis, carcinoma, tuberculosis and others, as it often does

Two of 10 new patients reported on from Kansas City recovered¹⁸⁵ Of the 10, 7 failed to react positively to the histoplasmin skin test Histoplasmosis must be considered as a possibility in cases in which there is roentgenographic evidence of widespread, coarse, parenchymal pulmonary shadows¹⁸⁶

Rawson and his associates¹⁸⁷ emphasize the frequency with which histoplasmosis affects the adrenal glands and causes symptoms of acute adrenal insufficiency The glands were involved in about 20 per cent of the cases thus far reported, and in 9 instances symptoms of adrenal insufficiency were present

The fear often arises that the application of various skin tests for diagnosis may complicate matters by causing specific hypersensitivity In regard to histoplasmin and antigens of other funguses, Howell's¹⁸⁸ study justifies the suspicion inasmuch as guinea pigs given intradermal injections with undiluted antigens are often sensitized thereby even to the point of cross reactions with antigens of different funguses In another study generalized infection seldom developed in Howell's guinea pigs after

183 Furcolow, M L , Bunnell, I L , and Tenenberg, D J A Complement Fixation Test for Histoplasmosis, Pub Health Rep 63 169-173 (Feb 6) 1948

184 Reimann, H A , and Price, A H Histoplasmosis in Pennsylvania, Pennsylvania M J , to be published

185 Bunnell, I L A Report on Ten Proved Cases of Histoplasmosis, Pub Health Rep 63 299-316 (March 5) 1948

186 Holt, J F Roentgenographic Pulmonary Manifestations of Fatal Histoplasmosis, Am J Roentgenol 58 717-723 (Dec) 1947

187 Rawson, A , Collins, L H , and Grant, J L Histoplasmosis and Torulosis as Causes of Adrenal Insufficiency, Am J M Sc 215 363-371 (April) 1948

188 Howell, A , Jr Studies of Fungus Antigens III Sensitization of Normal Animals with Skin Test Antigens, Pub Health Rep 63 595-601 (May 7) 1948, Isolation of Pathogenic Fungi from Experimentally Inoculated Guinea Pigs, *ibid* 63 602-616, 1948

intraperitoneal inoculation of the histoplasma organism¹⁸⁹ The development of specific hypersensitivity of the skin was not related to the size of the inoculum, and the fungus could be recovered from the spleen ten months later even in animals which remained well¹⁸⁹

Ringworm—Attention is again called¹⁹⁰ to the recent epidemics of ringworm of the scalp, epidemic tinea capitis The disease is commonest among poorer classes and is often unrecognized or misdiagnosed The disease should be one which, under the law, must be reported to public health offices Its control depends on early diagnosis and early thorough treatment

MALARIA

After fifteen years of search, the preerythrocytic stage of *Plasmodium vivax* was found and described by Shortt¹⁹¹ Based on studies on malaria in monkeys, biopsy of the liver was performed on a patient seven days after infection was brought about by inoculation of sporozoites from infected mosquitoes Sections showed plasmodial masses studded with chromatin particles like those seen in monkey's liver Colonel Shortt was awarded the Laveran prize at the Fourth International Congress of Tropical Medicine and Malaria for this important discovery His observations were confirmed by Hawking and his group¹⁹² working with monkeys When sporozoites are injected they can be traced for two to four hours, but thereafter they disappear and cannot be detected by subinoculation until after eight days During this period the parasite in the preerythrocytic stage is found in the liver Excellent illustrations are found in the paper

Part 2 of the May issue of the *Journal of Clinical Investigation* contains twenty-three papers on malaria chiefly devoted to the newer anti-malarial drugs The view that "pamaquin" ("plasmochin") may act as a true prophylactic agent in most persons infected with the Southwest Pacific strain of vivax malaria was confirmed (Alving) Several other compounds were equally effective when given in maximal dosage The compounds apparently act on the parasite in the preerythrocytic stages "Pamaquin" in maximum doses (Berliner) is not able to interrupt the erythrocytic schizogonous cycles of vivax and falciparum malaria Cura-

189 Howell, A The Efficiency of Methods for the Isolation of Histoplasma Capsulatum, Pub Health Rep 63 173-178 (Feb 6) 1948

190 Lee, R K C Epidemic Tinea Capitis A Public Health Problem, Pub Health Rep 63 261-268 (Feb 27) 1948

191 Shortt, H E , Garnham, J C C , Covell, G , and Shute, P G The Pre-Erythrocytic Stage of Human Malaria, Plasmodium Vivax, Brit M J 1 547 (March 20) 1948

192 Hawking, F , Perry, W L M , and Thurston, J P Tissue Forms of a Malaria Parasite, Plasmodium Cynomolgi, Lancet 1 783-789 (May 22) 1948

tive effects depend much on the strain of plasmodia dealt with. Pentaquine (SN-13,276), a quinoline compound closely related to "pamaquin," was effective in reducing the relapse rate in experimentally infected volunteers. The curative properties are enhanced by giving quinine at the same time, but even the combined drugs failed to prevent relapse in certain heavily infected volunteers. The toxicity of pentaquine is too great to warrant its use over prolonged periods, but on the basis of equal weight it is less toxic than "pamaquin" and has greater curative ability. At the Fourth International Congress on Malaria in May 1948 Alving announced isopentaquine (SN-13,274) as a safer and more effective drug in equal dosage. "Paludrine," a pyrimidine derivative, is also valuable for treating an acute attack of malaria and has little or no toxicity in doses much greater than those needed to suppress an attack. According to Earle and his co-workers, "paludrine" is the most active suppressive drug for vivax malaria ever synthesized. It is less active as a suppressive in falciparum malaria but is of greater value in prophylaxis. Berliner and his co-workers describe an effective method for detecting minimal numbers of plasmodia in the blood.

Trichinosis—The problems of preventing trichinosis were discussed by a committee.¹⁹³ While freezing for a number of days kills trichinae in pork, its commercial application is at present unfeasible because of lack of facilities and increased cost. Freezing also spoils the appearance of pork. If garbage were cooked before being fed to hogs, it would prevent infection, but cooked swill is said to be less palatable to hogs, and the process is expensive and hard to enforce. The committee nevertheless recommends the use of cooked garbage for hog feeding, prohibition of sale of pork from hogs fed untreated garbage, supervision of meat customarily eaten uncooked and education as to the need for cooking pork thoroughly.

Trichina worms may persist in the human intestine much longer than is generally believed. Stryker¹⁹⁴ reports a fatal case in which living gravid female worms were found in the intestine fifty-four days after the ingestion of pork. It is obvious that they may persist there even longer. This observation gives a clue to the persistence of the disease in certain instances wherein the continued release of larvae takes place.

Hetrazan, a new compound (1-diethylcarbamyl-4-methyl piperazine hydrochloride) which also gives promise of success in the treatment of

193 Control of Trichinosis, report of the Committee on Public Health Relations, the New York Academy of Medicine, Pub Health Rep 63 478-488 (April 9) 1948

194 Stryker, W. A. Intestinal Phase of Human Trichinosis, Am J Path 23 819-828 (Sept) 1947

filariasis, reduces the number of adult trichina worms in rats¹⁹⁵ It may be of value in the treatment of human trichinosis The drug acts on *Ascaris* in the intestine as well

Leptospirosis—The disparity of the number of cases of leptospirosis or Weil's disease recognized in this country as compared with European countries suggests that the disease is less common here, but it is more likely that it is often unrecognized Seventy-eight cases from the Detroit area are listed¹⁹⁶ In almost all instances previous contact with rats or dogs was evident Poultry handlers are often affected, and in 1 instance leptospiras were demonstrated on their work tables The relationship between *Leptospira icterohemorrhagia* and *Leptospira canicola* is not clarified It seems probable that not only the dog but also the rat may transmit *L. canicola* According to Bernkopf,¹⁹⁷ however, chickens themselves may be the source of infection in poultry handlers and others Chickens are susceptible to infection with the bovine strain of leptospiras

In patients with a benign form of meningitis leptospirosis as a rule would not even be suspected unless the disease were in mind Buzzard and Wylie¹⁹⁸ point out that meningitis occurs much more often in patients with leptospirosis who contract the infection by bathing in polluted water It is presumed that the leptospira enter through the conjunctivas and the nasal mucosa

RICKETTSIAL DISEASES

The initial dermal lesion of rickettsialpox, a disease recently discovered in New York city, except for lesser severity, is similar grossly and histologically to the primary lesion of scrub typhus and of Marseilles fever¹⁹⁹ The maculopapular rash of rickettsialpox is histologically similar to that of other rickettsial diseases, but the infiltration of cells is much greater Rickettsias have not yet been demonstrated in the skin Laboratory diagnostic tests available are but time consuming and intricate Even the complement fixation test requires at least 2 specimens of blood taken at three or four week intervals if the reaction in the first specimen is

195 Oliver-Gonzalez, J, and Hewitt, R Treatment of Experimental Intestinal Trichinosis with 1-Diethylcarbamy 4-Methylpiperazine Hydrochloride (Hetrazan), Proc Soc Exper Biol & Med 66 254-255 (Oct) 1947

196 Molner, J G, Meyer, K F, and Raskin, H A Leptospiral Infections A Survey, J A M A 136 814-819 (March 20) 1948

197 Bernkopf, H Experimental Leptospirosis Infection in Chickens, Proc Soc Exper Biol & Med 67 148-149 (Feb) 1948

198 Buzzard, E M, and Wylie, J A H Meningitis Leptospirosa, Lancet 2 417-419 (Sept 20) 1947

199 Dolgopel, V B Histologic Changes in Rickettsial-Pox, Am J Path 24 119-126 (Jan) 1948

negative Microscopic examination of the eruption is the quickest test but of course is not strictly specific

Mice and cotton rats which survived infection with *Rickettsia orientalis* carried the agent in their blood for six hundred and ten days, which suggests that rodents may be the natural reservoir of scrub typhus, as with other rickettsioses²⁰⁰

Although only a few patients with typhus²⁰¹ were treated, it is believed that chloromycetin given orally in divided doses of 35 mg per kilogram of body weight may be of value in therapy

To discover possible unrecognized Q fever in Texas, complement fixation tests were made on the blood of 1,400 meat-packing-house employees²⁰² Titers of 1 64 were found in 1 2 per cent, 1 32 in 2 2 per cent, 1 16 in 5 6 per cent and 1 8 in 8 per cent, which suggests previous infection with the agent Complement-fixing antibodies persisted seventeen months after known attacks

Rickettsia burneti, the cause of Q fever, was found in raw milk from dairies in southern California where Q fever had been found to be endemic, but persons who contracted the disease rarely used milk from these dairies²⁰³ Drinking infected milk does not account for the transmission of the disease to the majority of patients Some other means are involved According to Lennette's statement at the recent meeting of the American Society of Tropical Medicine, sheep and goats may be sources of infection Gsell²⁰⁴ observed explosive outbreaks in a household and in several communities in Switzerland

Streptomycin was successful in the treatment of guinea pigs infected with Q fever, but no report has been encountered dealing with the use of para-aminobenzoic acid²⁰⁵ Knowledge of Q fever since its discovery in Australia in 1935 is summarized in a review²⁰⁶

200 Fox, J P, and Olitsky, P K The Long Persistence of *Rickettsiae* *Orientalis* in the Blood and Tissues of Infected Animals, abstracted, *Federation Proc* 7 305 (March) 1948

201 Smadel, J E, Leon, A P, Ley, H L, Jr, and Varelo, G Chloromycetin in the Treatment of Patients with Typhus Fever, *Proc Soc Exper Biol & Med* 68 12-19 (May) 1948

202 Strauss, E, and Sulkin, S E Studies on Q Fever Complement-Fixing Antibodies in Meat Packers at Fort Worth, Texas, *Proc Soc Exper Biol & Med* 67 139-141 (Feb) 1948 Sulkin, S E, and Strauss, E Studies on Q Fever Persistence of Complement-Fixing Antibodies After Naturally Acquired Infection, *ibid* 67 142-144 (Feb) 1948

203 Huebner, R J, Hottle, G A, and Robinson, E B Action of Streptomycin in Experimental Infections with Q Fever, *Pub Health Rep* 63 357-362 (March 19) 1948

204 Gsell, O Q-Fever (Queenslandfieber) in der Schweiz, *Schweiz med Wchnschr* 78 1-5 (Jan) 1948

MISCELLANEOUS

Periodic Fever—A curious phenomenon of cyclic recurrences of fever and a variety of other signs and symptoms occasionally lasting over thirty years was studied by Reimann²⁰⁷ In many cases prolonged search failed to reveal the cause The cycles of the episodes varied from one to four weeks, and in the intervals the patients were in good health Theories about the cause include various infections, disturbed function of endocrine glands, allergic response, psychic phenomena and the response to a fundamental rhythm of life Cyclic fevers have apparently puzzled physicians since the time of Hippocrates²⁰⁸ Studies by Putnam, Boyd and Mead²⁰⁹ reveal striking cyclic changes of parasitemia and recrudescences in patients inoculated with vivax malaria In certain patients progressively declining parasitemia was marked by unexplained twelve day cycles of recrudescences and in others by sixteen day cycles, generally over a period of seventy-two days after infection Gross²¹⁰ in India reports cycles of relapses in chronic malaria of about thirty-four days No explanation is forthcoming to account for the twelve and sixteen day cycles early in the disease and for the thirty-four day cycles in the chronic phase Gross believes the last to be related to endocrinologic influences and claims to have stopped relapses by the administration of testosterone to male patients

Mononucleosis—Hepatic involvement was present in almost all of Evans' 19 patients with infectious mononucleosis²¹¹ Evidence was obtained by chemical tests, by biopsy and at necropsy which was in agreement with the findings of others The resemblance of the disease to viral hepatitis is recalled Experimental attempts²¹² to transmit the disease to volunteers with blood and throat washings from patients were unsuccessful

205 Huebner, R J , Jellison, W L , Beck, M D , Parker, R R , and Shepard C C Q Fever Studies in Southern California, Pub Health Rep 63 214-222 (Feb 13) 1948

206 Q Fever, editorial, Ann Int Med 29 154-162 (July) 1948

207 Reimann, H A Periodic Disease A Probable Syndrome Including Periodic Fever, Benign Paroxysmal Peritonitis, Cyclic Neutropenia and Intermittent Arthralgia, J A M A 136 239-244 (Jan 24) 1948

208 Periodic Diseases, editorial, Lancet I 565-566 (April 10) 1948

209 Putnam, P , Boyd, M F , and Mead, P A Periodic or Cyclically Recurring Phenomena of Vivax Malaria Infections, Am J Hyg 46 212 (Sept 24) 1947

210 Gross, S J Male Hormones for the Prevention of Relapses in Malaria, Indian M Gaz 82 65-66 (Feb) 1947

211 Evans, A S Liver Involvement in Infectious Mononucleosis, J Clin Investigation 27 106-110 (Jan) 1948

212 Evans, A S Experimental Attempts to Transmit Infectious Mononucleosis to Man, Yale J Biol & Med 20 19-26 (Oct) 1947

Erythema Nodosum—Of 155 cases of erythema nodosum, 86 per cent involved women²¹³ About one half of the patients had infections of the respiratory tract, and in one half of those in which cultures were made hemolytic streptococci were present in the throat Contrary to prevalent ideas, tuberculosis was an uncommon antecedent and rheumatic heart disease a rare sequel Erythema nodosum is probably a manifestation of hypersensitivity caused by a variety of infections and chemical agents conditioned by local trauma and personal predisposition

Reiter's Disease—This disease continues to baffle observers An English physician²¹⁴ regards it as the same as abacterial pyuria, since arthralgia occurred in several of his patients with the latter malady He suggests that it may be a venereal disease Dunham and his co-workers²¹⁵ cultivated a filtrable virus in embryonated eggs from the urethral and conjunctival exudate of a patient which they state caused conjunctivitis when inoculated into mice

Pleurodynia—An epidemic of pleurodynia occurred in Boston in the late summer of 1947²¹⁶ Over 100 patients were studied in the Boston City Hospital Thousands of cases probably occurred, and most no doubt were mistaken for cases of pneumonia, influenza, poliomyelitis, mononucleosis, meningitis, gastroenteritis and other abdominal disease because of the diversity of signs and symptoms Unnecessary surgical operations may be performed

Sludged Blood—Knisely²¹⁷ proposes the term "sludged blood" for the conditions which cause clumping of erythrocytes during many infectious diseases The phenomenon may be the same as the well known one responsible for the increased sedimentation rate of erythrocytes²¹⁸ or may result from the shocklike condition described by Moon The clumping of red cells and of bacteria may be brought about by a change in the plasma proteins and an alteration of the surface of suspended particles Sludg-

213 Favour, C B, and Sosman, M C Erythema Nodosum, Arch Int Med **80** 435-453 (Oct) 1947

214 Bains, G H Relation of Abacterial Pyuria to Reiter's Syndrome, Brit M J **2** 605-608 (Oct 18) 1947

215 Dunham, J, Rock, J, and Belt, E Isolation of a Filtrable Agent Pathogenic for Mice from a Case of Reiter's Disease, J Urol **58** 212-215 (Sept) 1947

216 Finn, J J Pleurodynia Preliminary Note on an Epidemic in Boston, New England J Med **237** 621-623 (Oct 23) 1947

217 Knisely, M H Sludged Blood, Science **106** 431-440 (Nov 7) 1947
Clark, E R Comment on Knisely, Philadelphia Med **43** 963-965 (Feb 21) 1948
Sludged Blood, editorial, J A M A **136** 556-557 (Feb 21) 1948

218 Reimann, H A The Significance of Fever and Blood Protein Changes in Regard to Defense Against Infection, Ann Int Med **6** 326-374 (Sept) 1932

ing may be the effect of these changes. However, it is suggested that sludging causes interference with the flow of blood and may thus cause symptoms. It has been proposed (Clark), therefore, that attempts be made to prevent sludging. Such reasoning appears to be analogous with that formerly applied to fever. For many years a rise in the temperature was thought to be harmful, and antipyretic drugs were in vogue, but general opinion now looks on fever as a defensive mechanism against infection. Perhaps sludging has a similar teleologic usefulness. All diversions from the normal do not need "treatment."

Agglutination reactions to heterophile tests and bacterial antigens are greatly enhanced by using serum as a diluent instead of the usual salt solution.²¹⁹ The results seem to parallel earlier reports showing the agglutination-enhancing effect of viscosity brought about in serum by increase in the amount of globulin or by the addition of gum acacia.²¹⁸

Antibodies and the Thymus—To test whether the thymus gland might be of importance in making or storing antibodies because of its predominantly lymphocytic structure, experiments²²⁰ were made on thymectomized animals and on control ones. The results were negative, the thymus played no demonstrable role in the formation or storage of antibodies evoked by the antigens injected. Only slight evidence of formation of antibodies in the spleen was detected after subcutaneous injection of antigens, evidence for this was greater after intravenous injection. The authors infer that the theory that leukocytes are a source of antibodies is a recent one, but it was proposed many years ago.

Fagraeus,²²¹ from other studies, concludes that "reticuloendothelial elements produce antibodies, thereby developing into a type of cell with the morphological characteristics of plasma cells." Antibody production reached its maximum when numerous immature plasma cells were present in tissue culture and receded as maturity advanced. Antigens accumulated in places in which plasma cells subsequently developed. It would seem, as suggested years ago,²²² that different types of cells of the reticuloendothelial system all play a role in the formation of proteins of the blood and, to that extent, of antibodies as well.

219 Milzer, A., and Nathan, S. Enhancement of Heterophile and Bacterial Agglutination Titers by Means of Serum Diluent, *Proc Soc Exper Biol & Med* **66** 619-621 (Dec.) 1947

220 Harris, T. N., Rhoads, J., and Stokes, J. A Study of the Role of the Thymus and Spleen in the Formation of Antibodies in the Rabbit, *J Immunol* **58** 37-42 (Jan.) 1948

221 Fagraeus, A. The Plasma Cellular Reaction and Its Relation to the Formation of Antibodies in Vitro, *J Immunol* **58** 1-13 (Jan.) 1948

222 Reimann, H. A., Medes, G., and Fisher, L. The Origin of Blood Proteins, *Folia haemat* **52** 187-202, 1934

The increasing use of frozen food lockers is bringing about more contact of inexperienced persons with fresh meat in its preparation. Report²²³ of 5 cases of tularemia from pork, 3 of brucellosis from beef and 2 cases of erysipeloid is made.

Morton and his associates²²⁴ find that certain widely advertised organomercurial compounds like "mercurochrome," "merthiolate" and "metaphen" as supplied commercially are not effectively germicidal against hemolytic streptococci. They are apparently more toxic for certain tissue cells and leukocytes than for bacteria. Their report was promptly challenged by proponents of "mercurochrome"²²⁵ and "merthiolate"²²⁶. Nevertheless, Morton's views hold, despite slight differences of technic and of criteria used for evaluation.

223 Palm, J. M. Hazards of Butchering, *J. Indiana M. A.* 40: 1154-1156 (Nov.) 1947.

224 Morton, H. E., North, L. L., and Engley, F. B. The Bacteriostatic and Bactericidal Actions of Some Mercurial Compounds on Hemolytic Streptococci, *J. A. M. A.* 136: 36-41 (Jan. 3) 1948.

225 Brewer, J. H. Reduction of Infectivity of Certain Pathogenic Bacteria by "Mercurochrome," *J. A. M. A.* 137: 858-861 (July 3) 1948.

226 Powell, H. M. Antibacterial Action of "Merthiolate" Against Hemolytic Streptococci, *J. A. M. A.* 137: 862-864 (July 3) 1948.

Book Reviews

Ocular Therapeutics By Wm J Harrison, M D Price, \$3 50 Pp 112 Springfield, Ill Charles C Thomas, Publisher, 1947

Here is a concise list of medicaments used in modern ophthalmology The materials are classified under various headings such as miotics and astringents Description, properties, uses and directions are listed in a systematic manner The discussions seem up to date, and this little manual should be useful for quick reference

Advances in Internal Medicine Edited by Wm Dock and I Snapper Volume 2 Price, \$9 50 Pp 642 New York Interscience Publishers, Inc, 1947

The second volume of this series contains sections on electrocardiography, circulatory failure, angiocardiology and angiography, surgical treatment of hypertension, surgical treatment of tumors and chronic inflammation of the lung, insecticides, physiologic and medical aspects of aviation and deep-sea diving, penicillin in subacute bacterial endocarditis and other infections, Rhesus antigen, pernicious anemia and other megaloblastic anemias, nutritional requirements in disease and nutritional diseases in the Orient

The section on electrocardiography is excellent in presentation and illustration Since there is no other readily available source of all the material presented, this volume becomes more valuable In the section on circulatory failure the authors' concepts are presented Numerous charts add to the clarity of the presentation Some of the ideas are controversial

In the section on angiocardiology the method and clinical applications of contrast visualizations are discussed The illustrations are well chosen and as a whole are well reproduced The accompanying diagrams add clarity to the few plates which lack contrast

The surgical treatment of hypertension is reviewed from the standpoint of anatomy of the sympathetic nervous system, purpose, indications and contraindications and evaluation of results of sympathectomy The various operative procedures are compared

The surgical approach to bronchial adenoma, bronchogenic carcinoma, tuberculosis, bronchiectasis and lung abscess is briefly reviewed

The effectiveness, the methods of application and the toxicity of various insecticides are presented The greater part of the section is devoted to a discussion of DDT (dichlorodiphenyltrichloroethane)

The two sections on the use of penicillin present concise information on the assay, use, indications, dosage and methods of administration of penicillin The material presented and an extensive bibliography make these sections extremely valuable

Although the reviewer would like to have included other "advances" in internal medicine, this volume is recommended

Diseases Transmitted from Animals to Man By Thomas G Hull, M D Third edition Price \$10 50 Pp 571 Springfield, Ill Charles C Thomas, Publisher, 1947

This well known text has been revised extensively since the last edition, and new material has been added consisting of chapters on scrub typhus, Q fever, jungle yellow fever, lymphocytic choriomeningitis and certain other unusual diseases. Like all texts made up of chapters by different authors, the method of presentation of material varies widely, and the viewpoint is equally varied. As an illustration of this, one notes that although the relationship of hoof-and-mouth disease, contagious ecthyma of sheep and some of the fungi of animals to diseases of man certainly are questionable, these are given prominent attention whereas malaria, transmitted by animals (mosquitoes), receives a bare sentence. The statement that dogs and wild rodents act as reservoirs for *Leishmania donovani* and "probably constitute important sources for infection" would require considerable documentation before it could be accepted as fact. The method by which *Salmonella* infections are transmitted from animals to man is not elucidated, and these infections are not at all comparable to the diseases commonly considered as transmitted from animals to man. In the case of scarlet fever, one may with propriety ask if the disease is not one transmitted from man to animals rather than the other way around. There appears to be no reason for giving space to coccidioidomycosis, since the author himself reveals the fact that it is not transmitted from animals to man.

Trichomonas Vaginalis and Trichomoniasis By Ray E Trussell, M D, with an Introduction by E D Plass, M D Price, \$6 Pp 288 Springfield, Ill Charles C Thomas, Publisher, 1947

Although the subject of the trichomonas organism would on first thought hardly seem to justify a whole book, it certainly is useful to find between two covers all that is known to date about the biology and the disease-producing capacities of this interesting flagellate. The author has assembled a bibliography of 1,586 titles, and there is a critical discussion of over one hundred agents which have been claimed to be of value in *Trichomonas vaginalis* infections.

Kompndium der parasitischen Wurmer im Menschen By Hans A Kreis, M D Pp 133, with 70 illustrations Basel, Switzerland Benno Schwabe & Co, 1947 Distributor in United States, Grune & Stratton, Inc, New York

This little book makes no claim to originality. The author states that there is no similar compendium in the German language, and he has compiled this manual from a variety of sources. Points of note are the excellent illustrations, the key table to the identification of parasites and ova and the good paper and print. The book should have a wide use in countries in which German is spoken.

COCCIDIOIDOMYCOSIS

Persistence of Residual Pulmonary Lesions

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AND

R BERKE, M D

NEW YORK

NUMEROUS former military personnel of World War II (actual figures not available) have served in the southwestern desert area of this country, where coccidioidomycosis is endemic. The presence of these troops in large numbers has stimulated study of the disease. It is now known that about 80 per cent of the long time residents of the endemic area are infected and that about 25 per cent of the military personnel with several months' residence in the endemic area became infected.¹ From 20 to 25 per cent of infections are clinically recognizable.²

It is not the purpose of this paper to present a detailed discussion of such factors as the etiologic agent (the fungus *Coccidioides immitis*) and its life cycle, the pathogenesis or racial differences in incidence. These and other fundamental data have already been described amply in the literature. The primary purpose is to present data on a series of patients residing in New York city with protracted residual pulmonary lesions of coccidioidomycosis and to discuss the pitfalls in diagnosis. Although it has been estimated³ that roentgenoscopy shows

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1 Smith, C E, Beard, R R, Rosenberger, H G, and Whiting, E G. Effect of Season and Dust Control on Coccidioidomycosis, *J A M A* **132** 833 (Dec 7) 1946.

2 Smith, C E, Beard, R R, Whiting, E G, and Rosenberger, H G. Varieties of Coccidioidal Infection in Relation to Epidemiology and Control of Diseases, *Am J Pub Health* **36** 1394 (Dec) 1946.

3 Conant, N F, Martin, D S, Smith, D T, Baker, R D, and Callaway, J L. *Manual of Clinical Mycology*, Philadelphia, W B Saunders Company, 1945, p 55.

pulmonary changes in 80 per cent of cases, no follow-up study of these changes in cases outside the endemic area has been reported previously

One of us (H E B)⁴ reported on a group of cases with pulmonary lesions, but these observations were limited to relatively recent infections. The case reports which follow constitute a two to five year follow-up study of various residual lesions of coccidioidomycosis. The patients forming the basis for this report were veterans of World War II who had returned to civilian life in New York city. In the majority of instances the diagnosis of pulmonary coccidioidomycosis

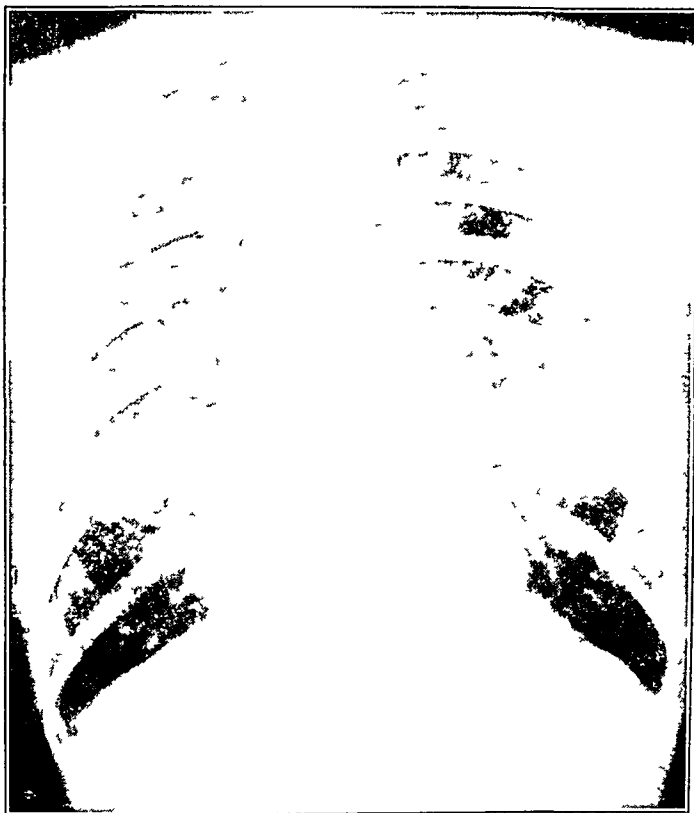


Fig 1—Solitary large cavity, with fluid level, in upper part of right lung field

had been made prior to discharge from military service. In several instances no definite diagnosis had been made. In some of the cases the condition had subsequently been diagnosed as tuberculosis or other pulmonary diseases. Twenty cases with various types of pulmonary residual lesions were encountered in this series. The importance of diagnosis, particularly of differentiation from pulmonary tuberculosis, will be emphasized in the case reports and in the discussion which follows. Thirteen of the more representative cases will be described.

⁴ Bass, H E, Kooperstein, S I, Friedman, M M, and Kastlin, G H. Pulmonary Coccidioidomycosis, *Dis of Chest* **12** 371 (Sept-Oct) 1946

REPORT OF CASES

CASE 1—Solitary large cavity A routine roentgenogram of the chest made at the time of discharge from the Army, in December 1945, showed a cavity in the right lung. The patient was asymptomatic. There was a history of contact with a tuberculous brother prior to induction, and the initial diagnosis was tuberculosis. Further history revealed six months' exposure in the California-Arizona desert in 1942. Specimens of sputum were negative for tubercle bacilli and fungi. Reactions to tuberculin tests were negative in all dilutions. The coccidioidin skin test gave a positive reaction in a dilution of 1:1,000. The serologic reactions were negative. The final diagnosis was coccidioidal cavity in the lung. A roentgenogram of the

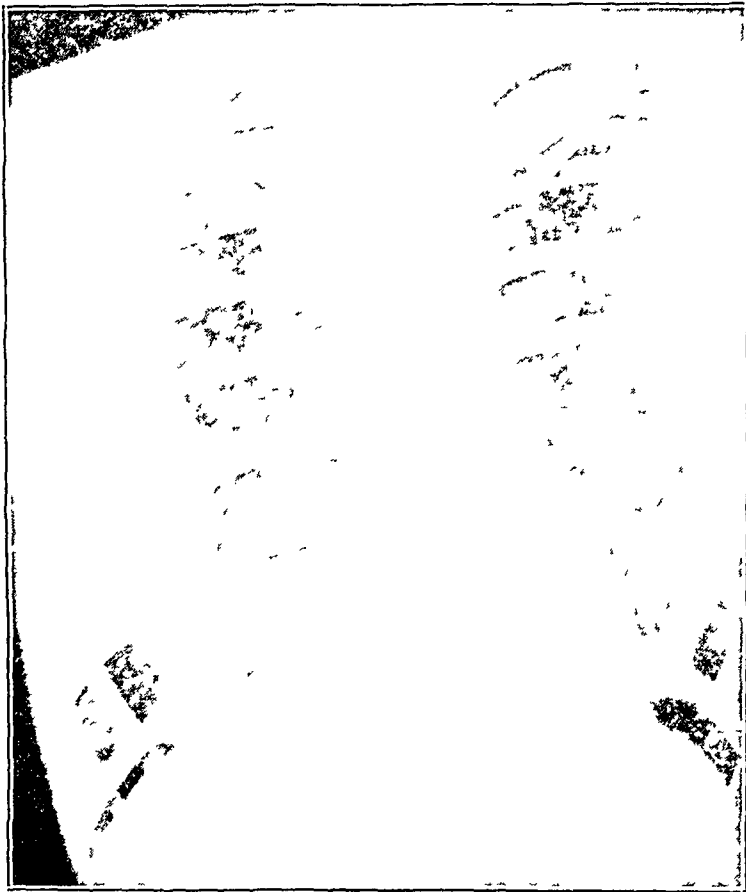


Fig 2—Single round area of density at left second rib anteriorly

chest on Sept 17, 1947 (fig 1) showed a large cavity, 5 by 4 cm, with a fluid level, in the upper part of the right lung. The cavity has not shown any change in two years of observation. The rest of the lung fields is normal.

CASE 2—Solitary round area of density The patient, a laboratory technician, had handled cultures from patients with coccidioidomycosis in an endemic area in Arizona. A routine roentgenogram of the chest made at a separation center in May 1946 showed a round area of density in the upper lobe of the left lung. The patient was asymptomatic. Reactions to both coccidioidin and tuberculin skin tests were positive. A roentgenogram of the chest taken on Oct 16, 1946 (fig 2) showed a round area of density, measuring 2 cm, at the left second rib anteriorly. A follow-up roentgenogram of the chest taken at the time of this report two years later, indicates no change in the area of density.

CASE 3—Small irregular area of density The patient underwent desert training in the California-Arizona maneuver area in 1942 and 1943. In August 1943 he experienced a sudden episode of weakness and pain in the chest. A roentgenogram of the chest showed bilateral pulmonary infiltrations and an increase in hilar density in the left lung. Reactions to both coccidioidin and tuberculin skin tests were positive. A roentgenogram of the chest taken on Oct 1, 1946 indicated a small, irregular area of density at the left first interspace anteriorly. A follow-up roentgenogram shows no change in the lesion in two years, the reaction to the skin test with coccidioidin remains positive.

CASE 4—Stationary apical cavity The patient, a 28 year old Negro, had been exposed to desert conditions near Phoenix, Ariz., from August 1942 to May 1943.

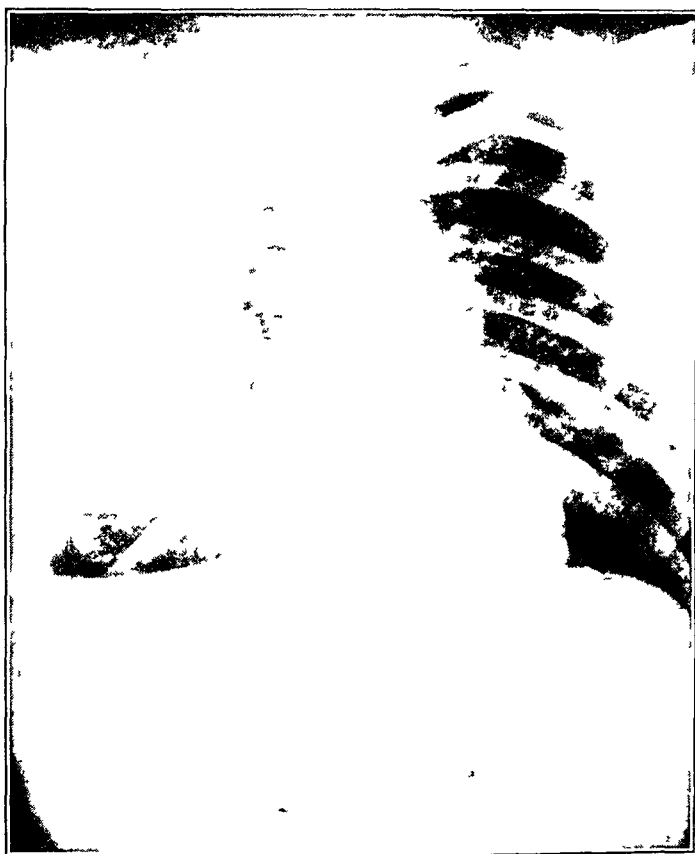


Fig 3—Encapsulated pleural effusion on right side of chest. Tubercle bacilli and *Coccidioides immitis* were recovered from the fluid.

He was discharged from military service in January 1946. The roentgenogram of the chest made at that time was interpreted as normal, but a routine preemployment roentgenogram, taken in May 1946, showed an apical cavity in the right lung. Reexamination of the separation film showed the same cavity. The patient was asymptomatic. The reaction to 10 mg of old tuberculin was weakly positive. The coccidioidin skin test gave a positive reaction. Specimens of sputum were negative for tubercle bacilli and fungi. A roentgenogram of the chest taken in the lordotic position showed a cavity, measuring 3 by 3 cm, at the apex of the right lung. The cavity has remained unchanged for two years, the rest of the lung fields is normal, and the reaction to the coccidioidin skin test is still positive.

CASE 5—Solitary round area of density The patient had been assigned to an air field near Tucson, Ariz, from July 1942 to October 1945 In March 1945 he experienced pain in the chest, fever, dyspnea and loss of weight and a cough developed A roentgenogram made on March 23, 1945 showed infiltration in the lower part of the left lung field and an increase in hilar density in the left lung The coccidioidin skin test gave a positive reaction Reactions to complement fixation and precipitin tests were positive A follow-up roentgenogram taken on Jan 28, 1948 showed a round area of density, 2.5 cm in diameter, still present in the lower part of the left lung field The density has not shown any change in almost three years, and the reaction to the coccidioidin skin test is still positive

CASE 6—Combined tuberculosis and coccidioidomycosis with persistent pleural effusion The patient served in the Arizona desert in 1943 Acute primary

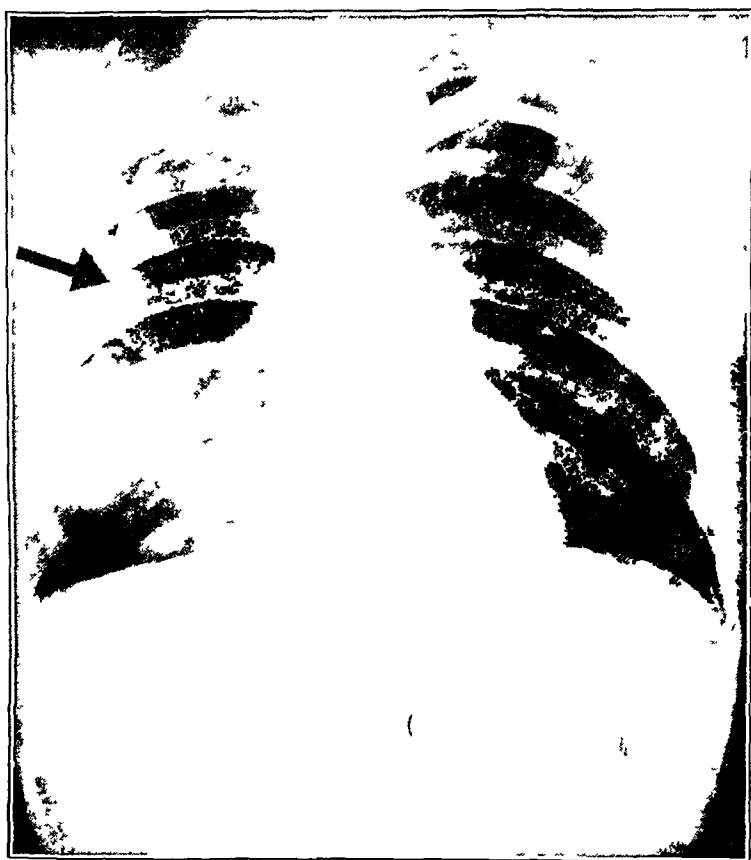


Fig 4—Hydropneumothorax on right side, round area of density at periphery of right lung, smaller round area of density at inner end of left third rib anteriorly

coccidioidomycosis developed in September 1943 Roentgenograms of the chest showed bilateral pulmonary infiltrations After partial resolution of these lesions, the patient was sent overseas In August 1945 a febrile episode occurred A roentgenogram showed hydropneumothorax on the right side Cultures of the chest fluid revealed tubercle bacilli and *C immitis* Guinea pig inoculations also gave positive reactions for both diseases, and reactions to tuberculin and coccidioidin skin tests were positive⁵ The patient came under our observation in October 1947

5 This was the status of the patient up to the point at which the case was reported by Rifkin and associates (Rifkin, H, Feldman, D J, Hawes, L E, and Gordon, L E Coexisting Tuberculosis and Coccidioidomycosis, Arch Int Med 79 381 [April] 1947)

A roentgenogram made on October 29 (fig 3) showed an encapsulated effusion of the right pleural cavity. After thoracentesis, a roentgenogram, on November 21 (fig 4), showed hydropneumothorax on the right side, with a round area of density, 2 cm in diameter, at the periphery of the right lung. There was a small, round area of density, also present on previous films, at the level of the left third rib anteriorly. The reaction to the coccidioidin skin test is still positive.

CASE 7—Small nodule with calcification. The patient underwent desert training in the California-Arizona maneuver area from August 1943 to January 1944. He was hospitalized for a ten day period in November 1943 for a condition diagnosed as "pneumonia." In August 1944, while he was in England, infectious hepatitis

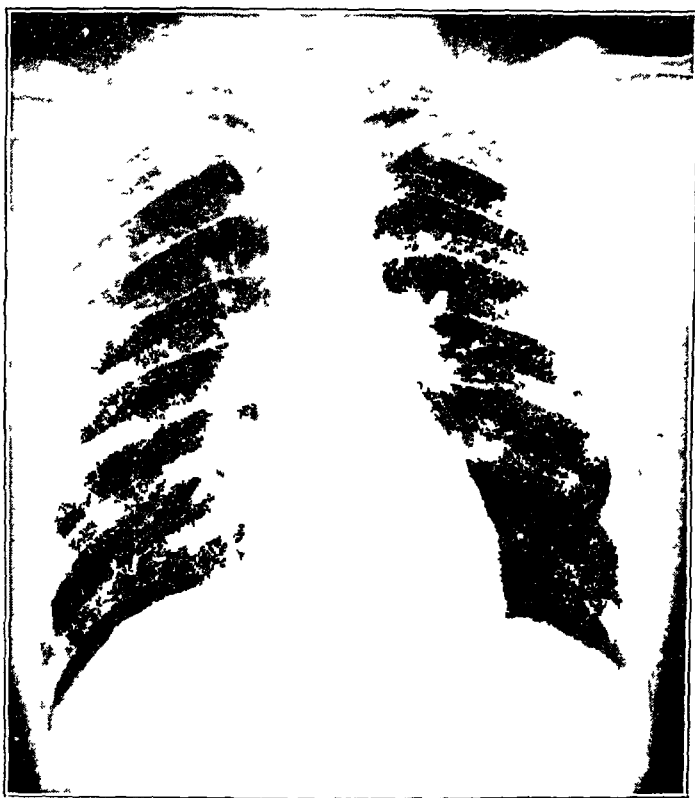


Fig 5—Thick-walled cavity behind right second rib anteriorly

developed. A routine roentgenogram of the chest showed a round lesion in the upper part of the left lung field. Tuberculosis was suspected, but reactions to all tuberculin tests were negative. The reaction to coccidioidin was positive in a dilution of 1:1,000, and the complement fixation test gave a positive reaction. A roentgenogram of the chest on Jan. 29, 1947 showed a small, round area of density with central calcification at the left first interspace anteriorly.

CASE 8—Bilateral cavities with spontaneous closure. The patient spent eight months in the Arizona desert in 1943. An acute infection of the upper respiratory tract developed while he was in the endemic area. In 1945, he had sudden hemoptysis while in the South Pacific. A roentgenogram of the chest showed thin-walled cavities in the upper field of both lungs. Reactions to skin tests with both coccidioidin and tuberculin were positive. Repeated examinations of the sputum failed

to reveal fungi or tubercle bacilli. Spontaneous closure of the cavities occurred in one year. A follow-up roentgenogram, taken on Sept 26, 1947, showed bilateral residual fibrosis.

CASE 9—Single thin-walled cavity and bilateral areas of fibrosis. The patient began desert training in West Texas in August 1944, fever, cough, pain in the chest and dyspnea developed two months later. A roentgenogram of the chest indicated a pneumonic infiltration in the right lung. Reactions to coccidioidin and tuberculin skin tests were positive, as were those to complement fixation and precipitin tests. A roentgenogram of the chest on Oct 24, 1946 showed a residual, thin-walled cavity at the right second interspace anteriorly and bilateral infraclavicular fibrosis. A follow-up roentgenogram, made on Jan 12, 1948, showed no change in the pulmonary cavity or in the rest of the lung fields. The reaction to the coccidioidin skin test is still positive, the serologic tests give weakly positive reactions.



Fig 6—Disseminated coccidioidomycosis of the skin, showing pink, erythematous, granulomatous plaques on left lower portion of posterior wall of chest.

CASE 10—Round area of density with central cavitation. The patient was stationed in the California-Arizona desert area from March to September 1943. A routine roentgenogram on his discharge from the Army, in December 1945, showed a cavity in the right lung. The coccidioidin skin test gave a positive reaction in a dilution of 1:1,000. Reactions to all tuberculin tests were negative, and specimens of sputum were negative for both fungi and tubercle bacilli. A roentgenogram of the chest on Sept 11, 1947 (fig 5) showed a cavity, measuring 3 by 3 cm, behind the right second rib anteriorly, comparison of this film with that of December 1945 revealed no change in the pulmonary lesion.

CASE 11—Solitary oval nodule. The patient served in the Arizona desert from February 1944 to March 1945. A routine roentgenogram of the chest made at the time of discharge, in July 1945, showed a nodular lesion in the right lung. Reactions to skin tests with coccidioidin and tuberculin were positive. A roentgenogram of

the chest made on May 19, 1947 showed an oval area of density at the right second interspace anteriorly. Follow-up roentgenographic studies show no change in almost three years.

CASE 12—Bilateral nodular densities mistaken for metastatic carcinoma. While stationed in the Arizona desert for seven months in 1943, the patient experienced a febrile episode for ten days and was treated for "pleurodynia." A routine roentgenogram of the chest in July 1945 revealed bilateral nodular densities. The patient was asymptomatic and was separated from military service. A roentgenogram on April 12, 1946 again revealed the nodular densities in both lungs. A diagnosis of metastatic carcinoma of the lungs was made. A complete hospital study did not



Fig 7—Mottled infiltration in upper parts of both lung fields

confirm this diagnosis. A roentgenogram made on Sept 3, 1947 showed an oval area of density in the left middle lung field and a small, round area of density in the right sixth interspace anteriorly. Reactions to both coccidioidin and tuberculin skin tests were positive. There has been no change in the pulmonary lesions in two and a half years.

CASE 13—Disseminated coccidioidomycosis. The patient was in the desert training area in California for three months in 1944. Ten months later, a cutaneous lesion developed on his back (fig 6). A routine roentgenogram of the chest showed bilateral subclavicular mottled infiltrations. A diagnosis of lichen planus and pulmonary tuberculosis was made. The cutaneous lesions were treated for one year but failed to respond. Biopsy of the skin, performed on April 30, 1947 showed a coccidioidal granuloma with spherules in the tissue section. Reactions to coccid-

iodin skin tests were negative (anergy). Complement fixation and precipitin tests gave positive reactions. At the time of writing, a roentgenogram of the chest (fig 7) still shows a mottled infiltration in the upper parts of both lung fields.

COMMENT

Several pertinent observations were made in the cases described here as well as in the other 7 cases which comprised the study.

1 The residual lesions were of all types, i.e., nodular densities, cavities, mottled infiltrations, fibrosis, pleural effusion and calcification.

2 These residual pulmonary lesions characteristically showed little or no change over a period of observation of from two to five years.

3 All patients gave a history of residence in the endemic area, varying from three months to two years.

4 Skin sensitivity to coccidioidin was observed to diminish with the lapse of time.⁶ However, Smith and associates⁷ asserted that sensitivity to coccidioidin is durable and that, although it may wane, its loss is usually slow. Thus, while a dilution of 1:1,000 commonly yields strong reactions in early cases, it was found preferable to employ 1:100 and 1:10 dilutions in our (residual) cases. All the patients in this series reacted to coccidioidin in 1:100 dilution. The reactions were usually of a mild type (1 or 2 plus), in contrast to the stronger type of reaction (3 or 4 plus) which one of us (H. E. B.)⁴ had seen in a large group of relatively early cases.

5 A negative reaction to the coccidioidin skin test was misleading in the presence of a disseminating lesion. In such an instance (case 13) the failure to react to coccidioidin was presumed to be related to anergy. However, serologic examination is usually diagnostic and can often be confirmed by recovery of the spherules in a tissue biopsy, from sputum or from draining sinuses.⁸

6 In cases of cavity formation, no evidence of bronchogenic spread or of seeding to other parts of the lung fields, such as occurs commonly in tuberculosis, was observed.

7 The resemblance of the residual pulmonary lesions to those in tuberculosis was striking. In several of the cases, a diagnosis of tuberculosis had been made after the patient's return to civilian life, usually after a routine chest survey or preemployment roentgenoscopic examination. In a number of cases, a positive reaction to both the tuberculin

6 Chenev, G. and Denenholz, E. J. Observations on Coccidioidin Skin Test, *Mil Surgeon* **96** 148 (Feb) 1945.

7 Smith, C. E., Whiting, E. G., Baker, E. E., Rosenberger, H. G., Beard, R. R., and Saito, M. T. The Use of Coccidioidin, *Am Rev Tuberc* **57** 330 (April) 1948.

8 Smith, C. E. Coccidioidomycosis, *M Clin North America* **27** 790 (May) 1943.

and the coccidioidin skin test made diagnosis difficult. In such cases a presumptive diagnosis of coccidioidomycosis was made on the basis of the following evidence: (a) history of exposure in an endemic area, (b) roentgenographic evidence of a pulmonary lesion, usually a solitary cavity or nodular density, which showed no change after months of observation, (c) indication of an identical lesion in the roentgenogram of the chest taken on separation from military service, (d) a positive reaction to the coccidioidin skin test, and (e) absence of tubercle bacilli.

8. Almost all the patients observed were asymptomatic. The notable exceptions included a patient with a cavity who had recurrent hemoptyses, a patient with pleural effusion (case 6) and the single patient with disseminated disease (case 13).

SUMMARY

Twenty veterans of World War II with residual lesions of pulmonary coccidioidomycosis have been observed. Thirteen cases are described.

The residual lesions persisted from two to five years after the initial infection.

The importance of differential diagnosis from other pulmonary diseases, particularly tuberculosis, is emphasized.

CONCLUSIONS

Coccidioidomycosis should no longer be considered a rare disease confined to a small endemic area (the San Joaquin Valley in California). At present the endemic areas in the United States include West Texas, southern New Mexico, southern and central Arizona, southwest Utah, and possibly southern Nevada, and a number of areas in southern California, in addition to the San Joaquin Valley.⁹ The incidence of infection in military personnel who spent part of their military service in the endemic areas was high (25 per cent). Increased travel facilities and the popularity of motor car travel (merely driving through an endemic area can result in infection) are additional factors of importance in the incidence of this disease.⁹ Any person who presents a pulmonary infiltration in which the diagnosis cannot be readily established should be questioned as to exposure in an endemic area. If such a history of exposure is obtained from one who reacts to coccidioidin, a presumptive diagnosis of pulmonary coccidioidomycosis should be made.

⁹ Smith, C. E. Recent Progress in Pulmonary Mycotic Infections, California Med 67:179 (Sept) 1947.

ANTIBIOTIC THERAPY FOR CUTANEOUS ANTHRAX

Report of Five Cases

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AND

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IT IS our purpose to outline the favorable results of treating cutaneous anthrax with penicillin and sulfadiazine in 4 cases and with streptomycin in 1. We think that this is the first report of the use of streptomycin in cases of human anthrax. Streptomycin used in vitro is successful¹

It is claimed that the incidence of anthrax is rising in the United States. A survey of the United States Public Health Service discloses the data in the accompanying table

Incidence of Anthrax

	1937	1938	1939	1940	1941	1942	1943	1944	1945	1946	1947
United States	65	54	57	79	105	97	72	49	44	36	64
Arkansas	0	4	0	2	0	2	1	1	0	0	7

The animal colonies in Arkansas have been heavily infected during late years in the lowlands, particularly in Arkansas and Cross Counties. New endemic areas have appeared about Nashville, which is unusual. In 1942, 3,000 cattle, horses and hogs were reported to have anthrax, and perhaps there were many more not reported. Fifteen thousand animals were given prophylactic inoculation against anthrax during that year. As the incidence of anthrax diminishes, farmers are not so attentive to immunization of their animals. At present about one eighth of the animals in the areas in Arkansas in which anthrax is prevalent are immunized.

For many years there has been a greater incidence of human anthrax in the United States in areas, i. e., the Atlantic seaboard, in which infected hides from foreign countries, Arabia and Egypt, were processed. The recent war naturally diminished the high incidence of anthrax.

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1 Miller, E S, Scott, E B, Noe, H A, Madin, S H, and Henley, T F. Chemotherapy of Experimental Anthrax Infections, J Immunol 53 371-379 (Aug) 1946

in the states of New York and Pennsylvania. But a false sense of security led to more frequent occurrence of anthrax in animals in the range states, and promiscuous distribution of cattle products by the black market possibly raised the incidence.

REPORT OF CASES

CASES 1, 2 and 3—C J, D J and C H were white men aged 29, 31 and 33. Two (aged 31 and 33) were brothers, and the youngest was a relative by marriage. On Sept 10, 1947, the three men saw a cow fall in a neighbor's pasture and on informing the neighbor were told that they could have the animal. They skinned the animal while it was still warm, and within twenty-four to forty-eight hours the malignant pustules and edema typical of anthrax lesions had begun to develop. The other initial symptoms were severe headaches, malaise and high temperature. The lesions were multiple in all cases on the hands and forearms and were at the site of previous abrasions from briar scratches or lacerations incurred in skinning the animal. There was regional adenopathy. The 31 year old man had symptoms first, and he was taken to a local physician, who gave him several injections of penicillin which did not alter the appearance of the lesions. Lesions developed on the other 2 men on September 13, and all 3 were sent to the isolation ward at the University of Arkansas Hospital. The diagnosis was made from smear, culture and the typical appearance of the lesions. Cultures were sent to the bacteriology laboratory for study of the sensitivity of the organisms to penicillin and streptomycin. They were sensitive to both. In the 3 cases penicillin, 50,000 units every three hours intramuscularly, and sulfadiazine, 4.0 Gm initially and 1.0 Gm every four hours for five days, were administered, and the lesions were treated locally with gentian violet and dry dressings to prevent further spread of infection. In all cases the symptoms disappeared and the malignant edema was absent after forty-eight hours of treatment. The patients were discharged on the eighth day from the hospital, the lesions were dry and much smaller than they were on admission, and the smears were sterile.

CASE 4—E H, a 27 year old white woman, was the wife of patient C H (case 3). She had not come in contact with the animal that the three men had skinned, nor had she come in contact with the instruments used. She had dressed the anthrax lesions of her husband on Sept 14, 1947. On September 16 a typical lesion of anthrax developed at the site of a healing paronychia of her left middle finger. Smears of this lesion yielded the organisms of anthrax. The lesion was treated locally with gentian violet and bandaged, and the patient was given penicillin in oil and white wax intramuscularly, 300,000 units daily, and sulfadiazine, 4 Gm for the initial dose, and 1 Gm every four hours, as an outpatient and confined to her quarters. The treatment was continued for five days, at which time the swelling and tenderness had disappeared and the lesion was healing rapidly. Epitrochlear and axillary adenopathy had disappeared at this time.

CASE 5—A 15 year old boy was a butcher's helper. He helped to skin an animal that had died of what later was proved to be anthrax by the state veterinarian. Thirty cattle had died from anthrax in the area during the months of September and October. On Oct 12, 1947, the patient noticed a small vesicular lesion on the volar surface of his right forearm. By October 13 this lesion had become extremely dark and there was considerable swelling for several inches.

around the dark center. There was regional adenopathy. That night the patient began to have fever, and he felt exceedingly ill. He was admitted to the hospital on October 16, after a diagnosis of anthrax had been made by the local physician. Smear and cultures did not reveal the presence of anthrax, and agglutination tests for tularemia gave negative results. The principal symptoms on the patient's admission to the hospital appeared to be typical of anthrax, and there were malignant pustules, malignant edema and lymphadenopathy of the right axillary region. The temperature was 99.6 F, the pulse rate 120 and the respirations 20. The patient had a preexisting and apparently unrelated chronic glomerulonephritis. In view of the renal disease, which might have been complicated by sulfonamide therapy, and on the basis of successful eradication of anthrax in animals with streptomycin, it was decided to treat the patient with the latter drug. Within twenty-four hours after an initial dose of 500 mg intramuscularly and 250 mg every three hours for five days the patient was definitely improved. The edema had almost disappeared, and slight fever continued only twelve hours longer. The axillary lymphadenopathy had disappeared on October 22. The patient was discharged on the tenth day, the dry desquamating area, 3 cm across, had a small eschar thereon.

The patients in cases 1, 2, 3 and 4 were given daily 300,000 units of penicillin and sulfadiazine for five days. Improvement started within twenty-four hours and continued thereafter. This amount of penicillin was large compared with that given by Murphy and others,² which was roughly 325,000 to 475,000 units during seventy-five hours only. Cultures of material from their patients became sterile as early as the second day and usually by the fifth day of therapy. Smears usually are sterile before this. Ellingson and others,³ using 1,000,000 to 4,000,000 units of penicillin in 25 cases of cutaneous anthrax, in 3 of which bacteremia was also present, demonstrated sterile lesions in 21 cases. Unfortunately, our only bacteriologic check was the demonstration of sterile smears on the eighth day in the first 3 cases. However, the improvement in all 4 was quick in onset and progressively more notable daily. We did detect some evidence of the "tissue damaging factor" of *Bacillus anthracis*,³ but it was only slight. This damage, probably due to the toxin, continues to operate for a short time after the organisms have been killed by the penicillin.

We realized that the diagnosis of anthrax was not clearly proved in case 5 because smears and cultures did not reveal the disease. Since the history, the physical findings, the number of deaths from anthrax in animals and the laboratory tests ruled out other causes, we have no doubt that the lesions were due to this disease.

2 Murphy, F. D., La Boccetta, A. C., and Lockwood, J. S. Treatment of Human Anthrax with Penicillin. Report of Three Cases, *J. A. M. A.* **126**: 948-950 (Dec 9) 1944.

3 Ellingson, H. V., Kadull, J. P., Bookwalter, H. L., and Howe, C. Cutaneous Anthrax. Report of Twenty-Five Cases, *J. A. M. A.* **131**: 1105-1108 (Aug 3) 1946.

Miller and his collaborators¹ showed that 93 per cent of mice infected with anthrax survived when adequately treated for seven days with penicillin and 5 per cent survived when treated for seven days with sulfadiazine. We cannot find a previous reference to the use of streptomycin for human anthrax, and we are of the opinion that this is the first such report. Culturally, this antibiotic prevents the growth of the anthrax bacillus.

Our dosage of streptomycin was in keeping with the normal amount recommended for its proper usage. It will be noted that the patient's toxicity and the malignant appearance of the lesions improved greatly within the first twenty-four hours, the fever disappeared after thirty-six hours and axillary lymphadenopathy was barely palpable, the areas being no longer tender, by the sixth day of treatment with streptomycin. The renal lesion slowly improved and was not aggravated. It is possible that the dosage of the drug and the duration of its administration could have been decreased.

COMMENT

In our cases the cutaneous anthrax may have been naturally mild. How much time would have been required for a spontaneous uncomplicated cure is problematic. While we combined sulfadiazine with penicillin and recognized the effectiveness of either in this disease,² it is our feeling that the latter is the more efficient of the two and that we could have dispensed with the use of sulfadiazine. Some feel that the combination of a sulfonamide compound with penicillin is the most desirable therapy. Gold⁴ stated that sulfathiazole is the most effective of the sulfonamide drugs. Exactly what penicillin alone would do for the majority of septicemic and pulmonic forms is difficult to predict, but the observations of Murphy and others,² who successfully treated 3 patients with the cutaneous form as well as septicemia, are most encouraging. The patient in our case 5 may also have had the septicemic form.

A choice between penicillin and streptomycin for therapy in human beings would at present probably favor penicillin for it has more effectively suppressed cultural growth of anthrax, it is more widely distributed and it costs less since only 100,000 to 200,000 units daily for five to seven days is required. As streptomycin is studied more in connection with anthrax, it may prove to be the better drug. A sensitivity test with the two antibiotics is very desirable when there is doubt, as, for instance, when a patient has cutaneous anthrax and septicemia. The anthrax cultures in cases 3 and 4 were sensitive as

⁴ Gold, H. Anthrax. Review of Sixty Cases, with Report on Therapeutic Use of Sulfonamide Compounds, *Arch Int Med* **70** 785 (Nov) 1942.

follows One cubic centimeter of positive nutrient broth culture (Difco medium) showed no growth with 3 units and some growth with $1\frac{1}{2}$ unit, of penicillin and no growth with 1/5,120 mg and some growth with 1/10,240 mg of streptomycin⁵ This result helped us choose streptomycin for therapy in case 5

SUMMARY

Five cases of cutaneous anthrax are briefly described Four patients were given daily 300,000 units of penicillin and 6 Gm of sulfadiazine for five days, the fifth received daily 2 Gm of streptomycin for five days No fatalities occurred, improvement was noted within twenty-four hours, and thereafter progress was rapid Review of the literature shows that doses of only 100,000 to 200,000 units of penicillin daily for three days have sterilized the lesions of cutaneous anthrax Longer treatment, however, is safer This is the first case report of the successful use of streptomycin for human cutaneous anthrax and the first report of transmission of anthrax from one human being to another by direct contact

⁵ Dr James T Culbertson, professor of bacteriology, University of Arkansas School of Medicine, specially carried out these tests

RESPIRATION AND CIRCULATION IN PULMONARY ANOXEMIA

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THE ANOXEMIA of pulmonary diseases differs from that found in persons at high altitude, mainly because arterial carbon dioxide tension and hydrogen ion concentration increase in the former and decrease in the latter. To estimate the importance of carbon dioxide and/or hydrogen ion in circulatory and respiratory adjustment, results in patients with Ayerza's disease were compared with those secured in patients with anoxic conditions without carbon dioxide retention, i.e., in patients at high altitude and in those with congenital heart disease.

At present some of the mechanisms of respiratory and circulatory regulation are not completely clear. It was thought that the comparative study of these functions in various types of anoxia could throw light on the subject. For that reason it was decided to investigate the circulatory and respiratory function in three different types of anoxia: (a) anoxic anoxia due to impairment of the pulmonary function, with low arterial oxygen tension and carbon dioxide retention, (b) anoxic anoxia due to shunt of blood from the right side of the heart to the left through unaerated channels, with low arterial oxygen tension without carbon dioxide increase, (c) anemic anoxia in which arterial carbon dioxide and oxygen tensions are normal, but tissular anoxia is present.

The present paper deals with pulmonary anoxia.

MATERIAL

Determinations were made on 18 patients with different degrees of pulmonary fibrosis and emphysema. Sixteen were male and two female, 2 of the former being smokers. All patients complained of cough for a long time and had had acute bronchitis repeatedly. Eight had also had asthmatic attacks.

All patients complained of dyspnea. In 16 cases there was a definite cyanosis, and in 8 there was a fully developed picture of Ayerza's syndrome.

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The diagnosis was made on the basis of clinical and roentgenologic examination. In table 1 are listed the main symptoms and signs in every case, and it can be seen there that 8 of the patients studied had heart failure. Several elements were considered for the diagnosis of cardiac failure: enlargement of the heart, gallop rhythm, tricuspid murmur, engorgement of the liver, high venous pressure and prolonged circulation time. Dyspnea, common among these patients, was considered as a sign of heart failure only if it was present at rest and in the absence of bronchial spasm. Since edema is frequently found among these patients in the absence of heart failure, this sign was considered only when it was extensive and was accompanied with hepatic engorgement and high venous pressure.

METHODS

All the determinations were made with the subjects under basal conditions. They were placed in bed in a comfortable, quiet room, and they rested for at least thirty minutes. In some cases the sitting position was used.

Arterial Blood—The femoral artery was punctured with a 1 mm bore needle and blood received in a 30 cc syringe coated with paraffin oil. It was immediately transferred under paraffin to a 50 cc tube which contained heparin solution (1 drop for each 10 cc of blood), mixed gently with a glass rod and finally transferred to a blood-sampling tube under mercury. The tube was sealed with mercury and kept in the refrigerator until analysis was made.

Tonometers—For the determination of the acid-base equilibrium and the oxygen capacity, only one tonometer is needed. All necessary determinations were made from the blood in the tonometer and from the arterial blood as drawn, as will be shown later. Enough oxygen and carbon dioxide were added to the tonometer to obtain pressures of 190 and 40 mm of mercury and oxygen tensions of 20, 30, 40, 60 and 190 mm, respectively. About 6 cc of blood was introduced in each tonometer and equilibrated with the gas in a water bath at 37 C during fifteen minutes. After the blood was transferred into sampling tubes under mercury, the pressure of the gases in the tonometer was measured with a small mercury manometer. Duplicate analyses of the carbon dioxide and oxygen were carried out in a Haldane apparatus. The oxygen and carbon dioxide pressures of the tonometer at the bath temperature were calculated with the formula

$$p\text{CO}_2 \text{ or } p\text{O}_2 = C (B - w + pp) \frac{273 + 37}{273 + t} \times \frac{V - 6 + 5}{V - 6}$$

in which $p\text{CO}_2$ and $p\text{O}_2$ indicate partial pressure of carbon dioxide and oxygen in millimeters of mercury, C content of carbon dioxide or oxygen in volumes per cent, B barometric pressure in millimeters of mercury, w vapor pressure at room temperature, pp pressure of tonometer (to be subtracted if negative), t room temperature in degrees centigrade, V volume of tonometer in cubic centimeters, 6 volume of blood present in the tonometer during equilibration and 5 volume of blood taken from the tonometer for analysis.

Equilibrated and arterial blood as drawn was analyzed for oxygen and carbon dioxide contents in a Van Slyke-Neill apparatus. Duplicate analyses were carried out using 1 or 0.5 cc of blood. Determinations agreed within 0.2 volume per cent of oxygen and 0.5 volume per cent of carbon dioxide.

TABLE 1—*Clinical Data on the Eighteen Patients Studied*¹

Case	Age	Sex	Lungs				Heart			Blood Pressure	Dyspnea	Cyanosis	Edema	Red Blood Cell Count
			Emphysema	Fibrosis	Asthma	Sclerosis of Pulmonary Branches	Enlargement of Right Ventricle	Dilatation of Pulmonary Trunk	Right Axis Deviation					
1	60	M	+	+++	—	+++	++	+	—	160/80	+++	++	++	6,100,000
2	46	M	+	+	—	+	+	+	+	130/90	++	+	—	5,800,000
3	33	M	+	+	—	+	+	++	—	180/120	+++	++	+	6,300,000
4	40	M	++	++	++	++	+	++	+	170/105	++	+++	+	7,300,000
5	49	M	+++	++	—	++	—	+++	—	150/105	++	+	—	5,600,000
6	55	M	++	+++	++	++	++	+	—	140/85	++	+	—	4,500,000
7	35	M	++	+	+++	++	+	++	+	170/110	+++	++	++	6,700,000
8	52	M	+	++	++	++	+	++	—	135/110	+++	+++	—	6,900,000
9	58	M	++	++	++	++	+	+	+	125/80	+++	+++	—	5,600,000
10	64	M	++	++	—	++	++	++	+	170/110	++	+++	++	7,690,000
11		M	++	+++	—	+++	++	+	+	125/70	+++	+++	+	6,400,000
12		M	+++	+++	—	+++	+++	++	+	135/85	+++	+++	++	6,410,000
13	51	M	+	+	++	+	++	+	+	155/110	+++	+++	+++	7,500,000
14	62	M	+	+++	—	++	+++	++	—	180/120	+++	+++	+++	6,900,000
15	54	M	++	+++	—	+++	+++	++	+	120/80	+++	+++	+++	7,400,000
16		M	++	++	++	++	+	++	+	220/115	+++	+	—	4,700,000
17	56	F	+	++	++	++	+	++	—	100/70	++	—	—	4,000,000
18	58	F	+	+++	—	++	+	++	—	160/100	++	—	—	4,300,000

* One plus sign indicates slight, 2 plus, mild, 3 plus, pronounced and 4 plus, severe

Calculation of Carbon Dioxide Tension and p_{H} of the Arterial Blood—With carbon dioxide and oxygen tension and content of the blood equilibrated into the tonometer as the known variables, the carbon dioxide tension of the arterial blood as drawn was calculated from its carbon dioxide content and oxygen saturation, Henderson's nomogram being used. The carbon dioxide content of plasma was calculated from the values of the carbon dioxide content of the blood at 40 mm of mercury and complete saturation, and the oxygen capacity of the blood by means of the cartesian chart constructed by Henderson and others¹. The p_{H} of plasma was calculated by the Henderson-Hasselbalch equation. Free carbon dioxide of serum was obtained from the carbon dioxide tension, with the use of the solubility coefficient of Van Slyke and his associates² and bicarbonates by subtracting free carbon dioxide from the total carbon dioxide content of the plasma. The value 6.11 for pK found by Dill, Daly and Forbes³ in normal serum at 37 C was used.

Oxygen Tension of the Arterial Blood—The oxygen tension of arterial blood was calculated by interpolating the oxygen saturation of the arterial blood in the oxyhemoglobin dissociation curve (corrected for the arterial p_{H}). A standard curve was used when no oxygen dissociation curve for the subject was available.

Oxygen Dissociation Curve—Points on the oxygen dissociation curve were obtained by equilibrating the blood into the tonometers with oxygen tensions of 20, 30, 40 and 60 mm of mercury and carbon dioxide tension of 40 mm. Other steps were carried out as described previously. The oxygen dissociation curve was plotted to show $\frac{\text{Hb O}_2 \times 100}{\text{Hb}}$ as a function of oxygen tension at $p_{\text{H}} 7.40$.

To correct for derivations from $p_{\text{H}} 7.40$ in the various tonometers, $\log 100 \frac{\text{Hb O}_2}{\text{Hb}}$ was

plotted as a function of $\log p\text{O}_2$. This logarithmic dissociation curve has the advantage over the usual curve in that the effect of a given change in p_{H} on $\log p\text{O}_2$ is the same for practically all values of $\log 100 \frac{\text{Hb O}_2}{\text{Hb}}$. According to Dill (in a

personal communication) a change of a unit in p_{H} will produce a corresponding change of 0.479 in $\log p\text{O}_2$.

Water in Plasma and Red Cells—The determinations were carried out on arterial blood equilibrated with oxygen and carbon dioxide in a tonometer at pressures of 190 and 40 mm of mercury, respectively. After equilibration, blood was transferred under oil to a 10 cc centrifuge tube described by Peters and Van Slyke⁴. After centrifugation at 3,000 revolutions per minute during forty-five

1 Henderson, L. J., Bock, A. B., Dill, D. B., and Edwards, H. T. Blood as a Physicochemical System. IX. The Carbon Dioxide Dissociation Curves of Oxygenated Human Blood, *J. Biol. Chem.* **87** 181, 1930.

2 Van Slyke, D. D., Sendroy, J., Hastings, A. B., and Neill, J. M. Studies of Gas and Electrolyte Equilibria in Blood. X. The Solubility of Carbon Dioxide at 38° in Water, Salt Solution, Serum and Blood Cells, *J. Biol. Chem.* **78** 765, 1928.

3 Dill, D. B., Daly, C., and Forbes, W. H. The pK of Serum and Red Cells, *J. Biol. Chem.* **117** 569, 1937.

4 Peters, J. P., and Van Slyke, D. D. Quantitative Clinical Chemistry, London, Bailliere, Tindall & Cox, 1932, vol. 2, p. 56.

minutes, the plasma was separated and a measured amount, about 1 cc., placed in a small weighing bottle. The upper portion of the packed cells was discarded and a sample of the bottom weighed in a weighing bottle. Cells and plasma were dried at 110 C to constant weight. Cell's water (H_2O)_c, in cubic centimeters of water per liter of cells, was calculated with the formula specific gravity equals 1.300—0.3 (water per gram of cells) ⁵

Chlorides—Chlorides were determined in the anaerobically separated plasma and red cells by the method of Van Slyke and Sendroy modified by Eisenman ⁶

Bicarbonates in Red Cells and Plasma—Blood was equilibrated into a tonometer with carbon dioxide at a pressure of 40 mm of mercury and oxygen at a pressure of 190 mm, being thereafter transferred to (a) a blood-sampling tube under mercury, (b) a hematocrit tube and (c) the anaerobic centrifuge tube described by Peters and Van Slyke. Sample c was centrifuged at 3,000 revolutions per minute during ten minutes to minimize the carbon dioxide loss. Analysis of carbon dioxide in the separated plasma and in the total blood was carried out in the Van Slyke-Neill apparatus and carbon dioxide content of the red cells calculated from these values, the hematocrit readings were determined with the following formula

$$(\text{TCO}_2)_c = \frac{(\text{TCO}_2)_b - (\text{TCO}_2)_s V_s}{V_c}$$

in which $(\text{TCO}_2)_c$, $(\text{TCO}_2)_b$ and $(\text{TCO}_2)_s$ indicate total carbon dioxide of the red cells (c), blood (b) and plasma (s) in volumes per cent and V_s and V_c volumes of serum (s) and cells (c)

p_H of Red Cells— $(p_{\text{H}})_c$ was calculated with the use of the Henderson-Hasselbalch equation. Free carbon dioxide of the cells was obtained from carbon dioxide pressure with the use of the solubility coefficient of Van Slyke, Sendroy, Hastings and Neill ² as recalculated by Dill, Daly and Forbes ³ at 37 C. The value used for pk'_c (oxygenated blood) was 6.04 as found by the latter authors.

r, the distribution of electrolytes between plasma and cells, was calculated as follows

$$r \text{ Cl} = \frac{(\text{Cl})_c}{(\text{Cl})_s} \times \frac{(\text{H}_2\text{O})_s}{(\text{H}_2\text{O})_c} \quad r \text{ BHCO}_3 = \frac{(\text{BH CO}_3)_c}{(\text{BH CO}_3)_s} \times \frac{(\text{H}_2\text{O})_s}{(\text{H}_2\text{O})_c}$$

$$r \text{ H} = \frac{(\text{H})_s}{(\text{H})_c} \times \frac{(\text{H}_2\text{O})_s}{(\text{H}_2\text{O})_c}$$

Respiratory Volume—Respiratory volume was determined in subjects already familiarized with the procedure while lying in bed in a comfortable, quiet room. Patients inspired room air or various gas mixtures through a mouth piece from a 600 liter gasometer, gas volume and cardiac and respiratory rates were taken every minute for twenty minutes. Correctness of the gas mixtures was controlled by analysis in a Haldane apparatus before and at the end of the experiment.

Lung Volume and Its Subdivisions—A Sanborn-Benedict metabolism tester was used, with the soda lime container outside the spirometer and with a bell capacity of 8 liters. All determinations were made with the subject in a sitting position. Vital capacity and reserve and complementary air were determined in

5 Horvath, S. M., Consolazio, W. W., and Dill, D. B. Syllabus of Methods of the Fatigue Laboratory, Harvard University.

6 Eisenman, A. J. A Note on the Van Slyke Method for the Determination of Chlorides in Blood and Tissue, J. Biol. Chem. 82: 411, 1929.

the usual way. The difference between the normal expiratory level and the level of maximal inspiration was computed as complementary air. Residual air was measured in duplicate with Christie's method⁷ as modified by Robinson,⁸ the subjects being connected to the spirometer while they were in the position of maximal expiration.

Gas analysis of the final mixture was carried out in duplicate in a Haldane apparatus, dilution or storage technics, with frequent testing for carbon dioxide, being used.

All volumes are expressed in liters of air saturated with water vapor at 37°C and the prevailing pressure (B T P S).

Alveolar An—A curved glass tube with a 20 mm bore and about 100 cc capacity was employed, it was connected through a three way stopcock to the mouth piece and with a Mueller water valve in the opposite end. The subject, with the mouth piece and the nose clip adjusted, was asked to blow toward the end of a normal expiration, the cock was turned back as expiration was completed and a sample withdrawn from the tube.

In cases in which there is respiratory disease it is often difficult for the patient to expire as fast as he is required. In such cases the amount of gas expelled was measured, and if it proved to be greater than 600 cc in four seconds the sample was secured at this time.

Serial Determinations of Alveolar An—Subjects were connected through a mouth piece and a three way cock to a long rubber tube attached to a recording spirometer. Four gas-sampling tubes, previously evacuated, were attached to sampling outlets on that part of the cock carrying the rubber tube. After the apparatus was flushed with alveolar air, the subject was asked to blow as fast and as far as he could. Gas samples were taken within the first six seconds after about 500, 900 and 1,300 cc of expired air had been received. In some patients the expiration was so slow that only two samples could be obtained in that period, the first after 500 cc was received and the last at the end of the six second period (the volume of air expired at the moment the last sample was taken was variable).

Cardiac Output—All determinations were carried out with the patients sitting in a comfortable armchair at an angle of 105 degrees and with flexed knees. In every case the patient had been previously trained to carry out the procedures.

The arteriovenous oxygen difference was determined with Grollman's⁹ acetylene method, four samples being taken during the rebreathing period. The gas analyses were performed in a Haldane apparatus equipped with a 12 cc burette and with a device for acetylene absorption.

The oxygen consumption was determined by the open circuit method using a 100 liter gasometer, the air being collected during ten minute periods. These data were also used to calculate the basal metabolic rate according to the normal standards of Aub and Du Bois and then to calculate the ratio of pulmonary ventilation to oxygen consumption (ventilation equivalent for oxygen), which we used to express as cubic centimeters of pulmonary ventilation for each cubic centimeter of oxygen absorbed under similar conditions.

7 Christie, R. V. The Lung Volume and Its Subdivisions. I. Methods of Measurement, *J. Clin. Investigation* **11** 1099, 1932.

8 Robinson, S. Experimental Studies of Physical Fitness in Relation to Age, *Arbeitsphysiol* **10** 251, 1938.

9 Grollman, A. The Determination of the Cardiac Output of Man by the Use of Acetylene, *Am. J. Physiol* **88** 432, 1929.

Blood Volume—Determinations of blood volume were carried out by the injection of Evans blue (T 1824) according to Gibson and Evans' method¹⁰, four samples were taken fifteen, thirty, forty-five and sixty minutes after the injection of the dye. Readings were made on separated plasma with the Evelyn photoelectric colorimeter.

Cells and total blood volumes were calculated from hematocrit values, the latter being obtained on heparinized blood after forty-five minutes of centrifugation.

Venous Pressure—This was measured in the arm, with the subject in the recumbent position, by the technic described by Lyons, Kennedy and Burwell¹¹.

Circulation Time—Intravenous injection of 5 cc of 20 per cent "decholin" solution was used for the arm to tongue circulation time, 0.2 cc of ether in 1 cc of sodium chloride solution was used for the arm to lung circulation time.

Statistical Treatment—In the statistical evaluation of the results, the following equations were used for the standard deviation, $\sigma = \sqrt{\frac{\sum d^2}{(n-1)}}$, for the

standard error, $\epsilon = \sqrt{\frac{\sum d^2}{n(n-1)}}$. In groups with less than 10 cases the equation employed for the calculation of ϵ was $\sqrt{\frac{\sum d^2}{(n-1)(n-1)}}$.

In comparison of the different groups, the standard deviation of the difference between the averages was calculated according to the equation $\sqrt{\epsilon_1^2 + \epsilon_2^2}$. The differences were considered statistically significant when they were equal to or greater than three times their standard error.

RESULTS

Alveolar Air—As is shown in table 2, the carbon dioxide tension of the alveolar air ranged from 38.6 to 63.9 mm of mercury, with an average of 51.8 mm. For a group of normal subjects of the same age (40 to 60 years), Robinson⁸ found a mean value of 41 mm, the upper value being slightly over 45 mm. In 12 of our 16 patients the alveolar carbon dioxide tension was found to be over 45 mm of mercury, in the remaining 4 it was within the normal range.

On the other hand, the oxygen pressure of the alveolar air ranged between 60.6 and 98.5 mm, with an average of 78 mm, being in 10 cases lower than 85 mm, the lowest value found by Robinson in the previously mentioned group of normal subjects.

These results are in accordance with the findings of Meakins and Davies (1925)¹² and of Christie¹³ in cases of emphysema and with

10 Gibson, J. G., Jr., and Evans, W. A., Jr. Clinical Studies of the Blood Volume. I. Clinical Application of a Method Employing the Azo Dye "Evans Blue" and the Spectrophotometer, *J. Clin. Investigation* **16** 301, 1937.

11 Lyons, R. H., Kennedy, J. A., and Burwell, C. S. The Measurement of Venous Pressure by the Direct Method, *Am. Heart J.* **16** 675, 1938.

12 Meakins, J. C., and Davies, H. W. Respiratory Function in Disease, Edinburgh, Oliver & Boyd, 1925.

13 Christie, R. V. The Elastic Properties of the Emphysematous Lung and Their Clinical Significance, *J. Clin. Investigation* **13** 295, 1934.

TABLE 2—*Lung Volume and Pulmonary Ventilation* *

Case	Respira- tory Rate, per Minute	Pul- monary Ventila- tion, L/Sq M	Tidal Air, Liters	Vital Capacity, Liters	Reserve Air, Liters	Comple- mental Liters	Residual Air, Liters	Func- tional Residual Air, Liters	Total Capacity, Liters	Residual Air, Total Capacity, per Cent	Basal Meta- bolic Rate, per Cent	Ventila- tion Equiva- lent, Cc O ₂	CO ₂ in Expired Air, per Cent	Alveolar Air CO ₂ , Mm Hg	O ₂ , Mm Hg
2	18	4.08	0.40	2.54	0.72	1.82	2.48	3.20	5.02	49.4	63.8	26.3	3.15	{ 62.1 63.8	{ 63.0 61.1
3	12	4.13	0.70	3.81	1.04	2.77	2.45	3.48	6.26	39.1	55.6	26.9	3.06	{ 38.6 46.8	{ 98.5 92.5
4	16	4.02	0.41	3.68	1.23	2.45	2.05	3.28	5.73	35.8	57.2	27.2	3.19	{ 47.5 45.6	{ 85.7 96.2
5	9	3.33	0.67	2.27	1.10	1.17	2.52	3.62	4.79	52.6	75.6	34.8	2.40	{ 11.4 63.0	{ 95.5 57.0
6	17	5.43	0.53	2.80	1.18	1.62								{ 63.9 61.4	{ 67.8 72.6
7	16	4.22													
8	11	4.08	0.50	2.41	1.06	1.35	3.04	4.10	5.45	55.8	75.2	24.1	3.33	{ 38.7 12.9	{ 95.4 87.0
9	18	4.69	0.42									23.8	2.78	{ 38.2 53.2	{ 97.0 73.1
10	{ 19 11 }	5.68	0.60	2.26 2.32	1.00 0.94	1.26 1.38	1.65	2.65	3.91	42.2	67.8	37.6	2.10	{ 52.6 49.3	{ 69.4 78.7
11	22	4.69	0.41	2.80	0.80	2.00	1.00	1.80	3.80	26.3	47.4	24.3	2.93	{ 15.7 63.6	{ 86.5 65.0
12	19	4.44	0.47	2.24	0.63	1.61	2.80	2.93	4.54	50.6	64.3	31.6	2.60	{ 47.9 47.3	{ 87.9 81.1
13	16	4.41	0.41	1.80	0.90	0.90	3.18	4.08	4.98	63.8	81.9	22.0	3.57	{ 53.6 56.0	{ 78.2 76.1
14	28	5.17	0.34	1.68	0.50	1.18	2.09	2.59	3.77	55.4	68.7	27.8	2.63	{ 61.6 40.0	{ 71.2 96.2
15	28	4.16	0.30	{ 1.34 1.46 }	0.56	0.90	2.22	2.78	3.68	60.3	75.5	25.4	2.96	{ 50.0 49.6	{ 82.2 92.2
16	11	3.93	0.70	3.21	1.26	1.95	2.57	3.83	5.78	44.5	66.2	21.3	3.59	{ 63.1 51.2	{ 62.8 80.7
17	20	4.53	0.27	1.45	0.70	0.75	1.95	2.65	3.40	57.3	77.9	35.0	2.68		
18				0.87											
Mean	17.2	4.43	0.47	2.35	0.90	1.55	2.27	3.15	4.70	48.5	67.5	28.1	2.92		

* All figures are averages from at least two determinations. Volumes are expressed at 37°C., prevailing barometric pressure and complete saturation with water vapor.

those of Ayerza, Solari and Berconsky,¹⁴ Arrillaga, Berconsky and Taquini,¹⁵ Houssay and Berconsky,¹⁶ Berconsky¹⁷ and Capdehourat¹⁸ in cases of Ayerza's disease

In a consideration of the reliability of the findings in regard to the composition of alveolar air secured in patients with pulmonary disease, technical difficulties and uneven distribution of the gases in the alveoli have to be discussed. Proper washing of the dead space is prevented sometimes by the small volume of the reserve air. We considered 500 cc the minimum amount of gas necessary to wash the dead space. In some cases expiration was so slow that in order to exhale 500 cc about four to five seconds were needed. As during this time oxygen is being consumed and carbon dioxide produced, the values obtained must differ from the true values. Duplicate determinations made the same morning may be markedly different according to the time at which the samples are taken and the depth and velocity of the expiration. Each value given in table 2 represents the average of several determinations.

In some patients of our series the composition of the alveolar air was investigated by serial sampling as described under "Methods." In order to compare normal persons with emphysematous subjects, the values of the first alveolar sample (taken when 500 cc of air had been expired) and the last (taken six seconds after the beginning of expiration) were chosen. The results are summarized in table 3. It can be seen that in both groups the last sample has a lower oxygen and a higher carbon dioxide content than the first one, the difference being greater in emphysematous subjects. The average values for first and last samples were 0.30 volume per cent for oxygen and 0.57 volume per cent for carbon dioxide in the normal group and 0.99 and 2.10 volumes per cent for carbon dioxide and oxygen, respectively, in the emphysematous groups.

Since no important changes in metabolic rate were observed in the patients, these results indicated that in emphysematous lungs the alveolar air is unevenly distributed. The average alveolar respiratory quotients were 0.80 and 0.77 for the first and last samples from the normal

14 Ayerza, L., Solari, L. A., and Berconsky, I. Cianosis por hipoventilacion alveolar en un "cardíaco negro" de Ayerza, *Rev. Soc. de med. int. y Soc. de fisiol.* **6**: 511, 1930.

15 Arrillaga, F. C., Berconsky, I., and Taquini, A. C. Síndrome de hipoventilacion alveolar, *Rev. Asoc. med. Argent.* **6**: 542, 1930.

16 Houssay, B. A., and Berconsky, I. Cianosis por hipoventilacion alveolar, *Cong. nac. de med., Actas y trab., Buenos Aires* **2**: 91, 1932, *Presse med.* **40**: 1759, 1932.

17 Berconsky, I. La función hemo-respiratoria en los "cardíacos negros de Ayerza," *Semana med.* **1**: 1569, 1933.

18 Capdehourat, E. L. La cianosis de los cardíacos negros de Ayerza, Buenos Aires, Aniceto López, 1934.

persons and 0.75 and 0.68 for those from the patients with pulmonary disease. Since the respiratory quotients of the expired air were the same in both groups, these results indicate that the samples came from underventilated areas and that hypoventilation is more severe in the last sampled alveoli. These results confirm the findings of Sonne and Roelsen.

The uneven distribution of the gas in the alveoli of patients with pulmonary disease had been studied as early as 1911 by Siebeck¹⁹ and

TABLE 3—Comparison Between Two Samples of Alveolar Air in Normal Persons and in Patients with Chronic Pulmonary Diseases*

Subject	Alveolar CO ₂ , per Cent			Alveolar O ₂ , per Cent		
	First Sample	Last Sample	Difference	First Sample	Last Sample	Difference
Normal Subjects						
M V	5.69	6.20	0.51	14.00	13.69	0.31
	6.17	6.41	0.24	14.82	14.07	0.75
J C F	4.55	5.05	0.50	16.34	15.61	0.73
	4.42	4.44	0.02	16.89	16.84	0.05
J R S	5.86	6.25	0.39	12.31	11.16	1.15
	5.65	5.87	0.22	13.11	13.11	0.00
M C	5.68	5.84	0.16	13.30	12.58	0.72
	5.52	5.80	0.28	14.19	13.78	0.41
A M	3.46	3.86	0.40	17.08	16.25	0.83
	3.63	3.94	0.31	16.74	16.00	0.74
Mean			0.30			0.57
Case	Alveolar CO ₂ , per Cent			Alveolar O ₂ , per Cent		
	First Sample	Last Sample	Difference	First Sample	Last Sample	Difference
Emphysematous Patients						
4	6.29	6.80	0.51	12.68	11.49	1.19
	5.93	6.78	0.85	13.69	11.46	2.23
5	5.91	6.68	0.97	14.23	12.60	1.73
7	6.37	8.80	2.43	12.13	7.58	4.55
13	6.20	6.97	0.77	12.80	11.43	1.37
	6.47	6.63	0.16	12.54	11.37	1.17
15	8.16	8.72	0.56	11.33	9.97	1.41
19	7.52	9.19	1.67	11.49	8.01	3.18
Mean			0.99			2.1

* The first sample was taken after 500 cc of gas had been exhaled and the last one six seconds after the beginning of the expiration.

more recently by Sonne (1934)²⁰ in patients with bronchial asthma and pulmonary emphysema. By fractional sampling of the alveolar air, Sonne showed that the alveolar oxygen and the respiratory quotient decrease more rapidly in these patients than in normal subjects. This

19 Siebeck, R. Ueber den Gasaustausch zwischen der Aussenluft und den Alveolen. III. Die Lungenventilation beim Emphysem, *Deutsches Arch f klin Med* 102:390, 1911.

20 Sonne, C. Respiratory Air Exchange in the Lungs Under Normal and Pathological Conditions. *Acta med Scandinav*, 1934, supp 59, p 348.

would indicate that the last portions of the exhaled gas come from poorly ventilated areas or from alveoli perfused with more than the normal amount of blood. Roelsen²¹ confirmed these results. Allowing these patients to take a single breath of hydrogen, he showed that the inhaled gas mixed incompletely in the lung and that the last-exhaled fraction came from poorly ventilated alveoli.

Darling and others²² studied the rate of removal of nitrogen from the lungs by means of oxygen inhalation and showed that 4 of 5 patients with emphysema exhibited a considerable degree of unequal mixing in the lungs.

Christie¹³ compared the composition of alveolar samples obtained with the Haldane and Priestly method in normal and emphysematous subjects with that of samples obtained with an automatic sampler which collected a small amount of air at the end of each normal expiration. For normal subjects, the results of the two methods agreed fairly well, but great discrepancies were observed in regard to the patients with emphysema, the Haldane method giving higher values for carbon dioxide pressure. This clearly indicates that the difference between the composition of the alveolar air expired in a normal breath and the composition of reserve air is greater in patients with emphysema than in normal persons. Evidence of poor mixing in cases of emphysema has also been presented by Bruns,²³ Hoover and Taylor²⁴ and Weiss²⁵.

The unequal distribution of the gas in the emphysematous lung is possibly greater than is indicated by the serial sampling because of the fact that only a small portion of the air in the lung can be investigated with this method. In case 15, for instance, only 200 cc was exhaled between the first and the last sample in different proportions. Since the composition of the alveolar air depends on the amount of blood

21 Roelsen, E. Fractional Analysis of Alveolar Air After Inspiration of Hydrogen as Method for Determination of Distribution of Inspired Air in Lungs. Examination of Normal Persons and Patients Suffering from Bronchial Asthma and Pulmonary Emphysema, *Acta med Scandinav* **95** 452, 1938, Composition of Alveolar Air Investigated by Fractional Sampling. Comparative Investigations on Normal Persons and Patients with Bronchial Asthma and Pulmonary Emphysema, *ibid* **98** 141, 1939.

22 Darling, R. C., Cournand, A., and Richards, D. W. Studies on Intrapulmonary Mixture of Gases. V. Forms of Inadequate Ventilation in Normal and Emphysematous Lungs, Analyzed by Means of Breathing Pure Oxygen, *J Clin Investigation* **23** 55, 1944.

23 Bruns, O. Die Bedeutung der spirometrischen Untersuchung von Emphysematikern und Herzkranken, *Med Klin* **6** 1524, 1910.

24 Hoover, C. F., and Taylor, L. The Ventilatory Function of the Lung in Emphysema and Asthma, *Arch Int Med* **15** 1 (Jan) 1915.

25 Weiss, R. Ueber der Durchmischungsverhältnisse in der Lunge bei der Bestimmung des zirkulatorischen Minutevolumens, *Ztschr f d ges exper Med* **61** 357, 1928.

perfusing the alveoli as well as on their ventilation, if the underventilated alveoli were also ischemic, hypoventilation would be underestimated with this method

The conclusion can be drawn that in the emphysematous lung the composition of alveolar gases is not uniform on account of unequal ventilation. This condition makes the use of the term "alveolar air" incorrect, since there are several "alveolar airs," according to the portion of the lung sampled

Pulmonary Ventilation—Results are summarized in table 2. The average ventilation was 4.43 liters per square meter of body surface, with values ranging from 5.68 to 3.33. In a series of normal subjects the average ventilation was found to be 3.65, $\epsilon \pm 0.09$, liters per square meter. The difference between the averages was 0.780 ± 0.174 , i.e., statistically significant. Robinson⁸ has studied pulmonary ventilation in normal subjects of different ages. His data were recalculated for persons between 40 and 60 years and a value of about 4 liters per square meter of body surface obtained. This would indicate that in emphysema the pulmonary ventilation shows a tendency to increase, although in most cases the individual values are within the normal range. This is in accord with the findings of Scott,²⁶ Meakins and Davies,¹² Hoover,²⁷ Staehelin and Schutze²⁸ and others. On the other hand, Berconsky¹⁷ found that pulmonary ventilation was definitely diminished in some of the patients studied by him. This appears clearly from the figures for carbon dioxide content of the expired air. However, the minute ventilation was increased in some of his patients. This slight tendency toward an increased ventilation in our cases is also reflected in the oxygen equivalent, which gives an average of 28.1, $\epsilon \pm 1.33$, as compared with 22.8, $\epsilon \pm 0.62$, in the normal group. The difference of 5.3 ± 1.47 is statistically significant. The carbon dioxide of the expired air was lowered by 2.92, $\epsilon \pm 0.117$, for the emphysematous group and by 3.75, $\epsilon \pm 0.09$, for a normal group. The difference of 0.810 ± 0.145 is significant.

This increased ventilation may be due to (a) cardiac decompensation or (b) asphyctic stimulus.

The first possibility cannot be ruled out in cases 12 and 15. On the other hand, the patients in cases 6 and 17, who had the highest oxygen equivalent and the lowest carbon dioxide content in the expired air, did not show any sign of heart failure. As will be considered later,

26 Scott, R. W. Observations on the Pathologic Physiology of Chronic Pulmonary Emphysema, *Arch. Int. Med.* **26**: 544 (Nov.) 1920.

27 Hoover, C. F. The Alveolar Air and Minute Volume of Air in Pulmonary Emphysema, *Tr. A. Amer. Physicians* **27**: 572, 1912.

28 Staehelin, R., and Schutze, A. Spirographische Untersuchungen an Gesunden, Emphysematikern und Asthmatikern *Ztschr. f. klin. Med.* **75**: 15, 1912.

the effect of anoxia on ventilation was investigated by comparing the ventilation when the subject was breathing air and when he was breathing pure oxygen. The decrease observed in all cases but one indicates that anoxemia is an important factor in the observed hyperventilation.

Respiratory Rate—As shown in table 2, the average respiratory rate was 17.2 respirations per minute. Rates of 15.5, 12.4 and 11.8 were found by Robinson in three groups of normal subjects of a mean age of 44, 52 and 63 years respectively. Conversely, for the tidal air the average value was 474 cc, lower than the values of Robinson⁸ and those found in the normal group studied by us. Diminution of the tidal air has been found by Hoover,²⁷ Scott,²⁶ Houssay and Berconsky,¹⁶ Christie,¹³ Berconsky¹⁷ and Capdehourat.¹⁸

When the composition of the alveolar air is compared with the pulmonary ventilation, one is struck by the fact that in spite of the slight hyperventilation the alveolar carbon dioxide is high and the oxygen low. The fact that in most of these cases the metabolic rate was normal indicates that the efficiency of the ventilation is decreased. Decrease of the tidal air, one of the conditions leading to poor ventilatory efficiency, was present in some cases, but in others the amount was normal. The ineffectiveness of ventilation in our cases must be explained by the unequal ventilation of the different parts of the lungs. As Sonne²⁰ pointed out, the fact that the alveolar respiratory quotients were lower than those found in expired air of the same subject suggests that in the first-evacuated alveoli the respiratory quotient must be higher. This effect could be produced if most of the alveoli evacuated at the beginning of expiration were hyperventilated and those evacuated toward the end hypoventilated. The hyperventilation of some areas will decrease the efficiency of the ventilation and simulate an increase in the respiratory dead space. In fact, if the dead space is considered as the amount of air in which the alveolar air has to be diluted to become expired air, the low carbon dioxide and high oxygen contents of the hyperventilated alveoli will increase the dead space beyond its anatomic limit. So the apparent dead space can be used as a measure of the difference between the composition of the deep alveolar air and that of air exhaled during a normal expiration, other things being equal. In both normal subjects and emphysematous patients a value similar to that for the effective dead space was calculated as follows. Ventilation and respiratory rate were measured during ten minute periods. At the end of these periods, alveolar air was taken as usual. Expired and alveolar air was analyzed, and from these values and the value for tidal air the dead space was calculated with the use of Bohr's formula. This has to be distinguished from the effective dead space calculated in the usual way. It approaches the effective dead space when the distribution of the gas in the lung approaches uniformity. The effective tidal air was obtained by subtract-

ing the dead space calculated in this way from the tidal air. The formula $\frac{\text{effective tidal air}}{\text{tidal air}} \times 100$ is a measure of the effectiveness of the removal of the gas in each breath. In table 4 the utilization of the tidal air in some of our patients is compared with that in normal subjects. It can be seen that in normal persons the utilization of the tidal air is about 60 per cent and in emphysematous persons 40 per cent. Berconsky¹⁷ has made a similar calculation, subtracting from the tidal air the effective dead space as found by the usual method. He found that healthy persons utilize 73 per cent of the tidal air and patients with Ayerza's disease 46 per cent, values close to those found by us.

The diminished utilization of the tidal air shown in table 4 is due to two factors: (a) shallower breathing in the emphysematous group and (b) simulated increase of the dead space. In our cases the latter factor was the more important one.

TABLE 4—*Effectiveness of Pulmonary Ventilation in Patients with Emphysema and in Normal Subjects*

Emphysema				Normal Persons			
Case	Tidal Air, Cc	Effective Tidal Air,* per Cent		Subject	Tidal Air, Cc	Effective Tidal Air, per Cent	
		CO ₂	O ₂			CO ₂	O ₂
4	530	48.7	44.9	J. D.	446	53.8	53.0
8	558	37.8	37.8	J. C. F.	610	66.0	61.8
10	573	39.6	29.3	C.	495	59.0	61.2
13	414	40.3	30.9	J. R. E.	938	73.8	69.0
15	276	36.6	35.1	M. I. C.	495	60.5	62.0
17	278	38.5	35.6	D. G.	511	57.0	56.0
Mean	438	40.2	35.6		582	61.7	60.5

* Effective tidal air was calculated by subtracting from the tidal air the apparent dead space (see text) calculated from CO₂ and O₂ values and expressing the result in percentage of the values for tidal air.

In the preceding discussion it was assumed that the increased dead space was simulated by the uneven distribution of the gas in the lung. As a matter of fact, similar results can be obtained if the anatomic dead space has increased. By serial sampling of the expired air, Christie and Loomis have tried to differentiate between a true increase of the dead space and the one simulated by the shunting of air into relatively ischemic alveoli. They did not find evidence of any true increase in the anatomic or physiologic dead space. Berconsky¹⁷ investigated the respiratory dead space in 10 cases of Ayerza's disease and found a mean value of 132, as compared with 171 found in normal subjects. As he pointed out, this is probably due to the diminution of tidal air. However, his results, as well as those obtained by Capdehourat,¹⁸ cannot be considered as conclusive on account of difficulties in getting true alveolar samples in these patients. The results obtained by Berconsky

showed that in spite of the diminution of the dead space the ratio of dead space to tidal air increased in his cases, which indicated that shallow breathing was the most important source of alveolar hypoventilation

We can summarize the facts as follows. The ventilation is slightly increased in these patients, but on account of the unequal ventilation of the alveoli and the decreased tidal air, the efficiency is low. This inefficient ventilation is responsible for the fact that despite the slight increase in the respiratory minute volume the alveolar gases have a higher carbon dioxide and a lower oxygen content than normal.

The Lung Volume and Its Subdivisions—The results are summarized in table 2.

Absolute Values—Vital capacity was found to be diminished, extreme values being 0.87 and 3.81 liters, with an average of 2.35. Only 5 of 15 patients had values above 2.6 liters, the lowest normal figure found by Kaltreider and others²⁹ in healthy males of similar age, and only 2 had values above 3.45 liters, the lowest value found by Robinson⁸ in age groups VII, VIII and IX, which correspond to our group.

The spiograms frequently showed the failure of the respiration to return rapidly to the previous level after a deep inspiration or expiration.

The decrease of the vital capacity seemed to be due to a reduction in complementary air (mean value, 1.55 liters), reserve air being maintained at about normal (mean value, 0.90 liter).

Tidal air will be considered later in relation to dead space and effective ventilation.

The residual air ranged between 1.00 and 3.18 liters, with an average of 2.27 liters. The figures are higher than those found by Kaltreider and others and by Robinson in normal men (0.54 to 2.29, with an average of 1.30 liters, and 0.66 to 2.39, with an average of 1.67 liters).

Functional residual air (midcapacity) ranged between 1.80 and 4.10 liters with a mean value of 3.15, being increased in several cases as compared with the standards of Kaltreider and others²⁹ and Robinson⁸ (1.09 to 3.05, with an average of 2.00, and 1.27 to 3.46, with an average of 2.39, respectively).

Total pulmonary capacity varied within normal limits when compared with Kaltreider's standards (3.62 to 7.61 liters), and it was diminished in 4 male subjects when compared with Robinson's (4.34 to 7.90 liters). The average in our series, 4.70 liters, was smaller than that in both series of normal subjects (5.37 and 5.95 liters).

Relative Values—The wide normal range makes the absolute value a doubtful index in judging abnormalities of these functions. Therefore, results expressed as percentage of the total capacity are also considered.

29 Kaltreider, N. L., Fray, W. W., and Hyde, H. V. The Effect of Age on the Total Pulmonary Capacity and Its Subdivisions, *Am Rev Tuberc* 37:662, 1938.

in the chart. The mean value for the relation of residual air to total capacity was 48.5 per cent, extreme values being 26.3 and 63.8, a significant increase when compared with Kaltreider's and Robinson's figures (average, 24.5 and 27.8 per cent respectively). In cases 3, 4 and 11 the levels fell within normal range. On the other hand, when the relation of functional residual air to total capacity was considered, there were increased values in all cases except case 11, the mean being 67.5 per cent.

These results agree with those obtained by Anthony,³⁰ Hurtado and others,³¹ Christie¹³ and Kaltreider and others³² in cases of pulmonary fibrosis and emphysema and with those of Berconsky¹⁷ in cases of Ayerza's syndrome.

Individual differences found in our series can be explained on the basis of the prevalent emphysema or fibrosis of the lungs. However, heart failure may influence the decrease in the vital capacity and total capacity of patients with Ayerza's disease.

No significant correlation was found in our cases between absolute or relative values of residual air or functional residual air and arterial oxygen saturation or alveolar air tensions.

Basal Metabolic Rate—Determinations of the basal metabolic rate were made on 14 patients. The rates were normal in half of them and moderately high in the other half. Metabolism in patients with Ayerza's disease has been studied by Berconsky¹⁷ who found slight increase in 5 of 7 cases and ascribed it to the presence of heart failure. In our group of 7 patients with normal metabolism 3 had heart failure and the other 4 had no sign of cardiac involvement.

Among the 7 patients with increased metabolic rate 4 had cardiac failure and 3 had not.

These results indicate that besides cardiac failure other factors such as respiratory dyspnea may cause an increase of metabolism in patients with chronic pulmonary disease.

30 Anthony, A. J. Untersuchungen über Lungenvolumina und Lungventilation, *Deutsches Arch f klin Med* **167** 129, 1930.

31 Hurtado, A., Fray, W. W., and McCann, W. S. Studies of Total Pulmonary Capacity and Its Subdivisions. IV Preliminary Observations on Cases of Pulmonary Emphysema and of Pneumoconiosis, *J Clin Investigation* **12** 833, 1933. Hurtado, A., Kaltreider, N. L., Fray, W. W., Brooks, W. D. W., and McCann, W. S. Studies of Total Pulmonary Capacity and Its Subdivisions. VI Observations on Cases of Obstructive Pulmonary Emphysema, *ibid* **13** 1027, 1934, VIII Observations on Cases of Pulmonary Fibrosis, *ibid* **14** 81, 1935.

32 Kaltreider, N. L., Fray, W. W., and Hyde, H. V. Further Studies of the Total Pulmonary Capacity and Its Subdivisions in Cases of Pulmonary Fibrosis, *J Indust Hyg & Toxicol* **19** 163, 1937.

BLOOD—Oxyhemoglobin Dissociation Curve—In 5 cases of Ayerza's syndrome four points on the oxygen dissociation curve of the arterial blood at 37 C and p_{H} 7.40 were secured. All the patients had severe anoxia, arterial oxygen tension ranging between 37 and 53 mm of mercury and oxyhemoglobin capacity between 25.96 and 30 volumes per cent. The values of the oxygen pressure at half saturation, at $(p_{\text{H}})_s$ 7.40 and at arterial $(p_{\text{H}})_s$ are given in table 5. It can be seen that the average oxygen tension at half saturation, 25.8 mm of mercury, does not differ appreciably from the values obtained in normal persons at sea level. On the other hand, as the arterial $(p_{\text{H}})_s$ of the group with Ayerza's disease is lower than that of the normal group, the curve at the arterial $(p_{\text{H}})_s$ is displaced to the right, and oxygen pressure for hemoglobin, or oxyhemoglobin, is increased. These findings suggest that the hemoglobin has not changed in this type of anoxemia.

TABLE 5—*Position of the Oxygen Dissociation Curve in Patients with Ayerza's Syndrome*

Case	pO ₂ for Hb = HbO ₂ Mm Hg *	
	$(p_{\text{H}})_s$ 7.40	Arterial p_{H}
2	25.5	28.5
4	25.0	27
10	27.5	29
12	24.5	26
15	26.5	29
Mean	25.8	27.9

*Values for pO₂ at half saturation are at 37 C for constant $(p_{\text{H}})_s$ 7.40 and for the p_{H} of the arterial blood as drawn.

Oxyhemoglobin dissociation curves were studied in 2 cases of emphysema by Meakins and Davies,¹² and no appreciable deviation from normal was observed. The position of the dissociation curve at high altitude has been investigated by Barcroft and others,³³ Buikov and Martinson,³⁴ Dill and others,³⁵ Keys and his associates³⁶ and, more

33 Barcroft, J., and others. Observations Upon the Effect of High Altitudes on the Physiological Processes of the Human Body, Carried Out in the Peruvian Andes, Chiefly at Cerro de Pasco, Phil Tr Roy Soc, London, s B **211** 351, 1923.

34 Buikov, K. M., and Martinson, E. E. Arkh sc biol (USSR) **33** 147, 1933, cited by Aste-Salazar and Hurtado.³⁷

35 Dill, D. B., Edwards, H. T., Folling, A., Oberg, S. A., Pappenheimer, A. M., and Talbott, J. H. Adaptations of the Organism to Changes in Oxygen Pressure. Physicochemical Changes in Human Body at Low Oxygen Pressure, J Physiol **71** 47, 1931.

36 Keys, A., Hall, F. G., and Barron, E. S. G. The Position of the Oxygen Dissociation Curve of Human Blood at High Altitude, Am J Physiol **115** 292, 1936.

recently, Aste-Salazar and Hurtado³⁷ The last-named authors were able to show a slight shift of the curve to the right, confirming the previous work of Keys and others

Oxygen Capacity of the Blood—Our results are summarized in table 7 It can be seen that in most cases the oxygen capacity is well above the normal range

The oxygen capacity of the blood in cases of emphysema has been investigated by Meakins,³⁸ Campbell, Hunt and Poulton,³⁹ Himwich and Loebel,⁴⁰ Kountz, Alexander and Dowell⁴¹ and Christie¹³ The values were within the normal limits in most cases but increased in some Hurtado, Kaltreider and McCann⁴² studied 24 cases of emphysema and 37 cases of pulmonary fibrosis The oxygen capacity of the blood was markedly increased in only 9 cases and was normal in the others Kaltreider, Hurtado and Brooks⁴³ found 16.2 Gm of hemoglobin per hundred cubic centimeters in a group of emphysematous patients and an average of 16.6 Gm in fibrotic patients as compared with 16.2 Gm of hemoglobin as the average value in a normal group

The oxygen capacity of the blood in patients with Ayerza's syndrome has been investigated by Ayerza, Solari and Berconsky,¹⁴ Arrillaga, Berconsky and Taquini,¹⁵ Houssay and Berconsky¹⁶ and Capdehourat¹⁸ Berconsky¹⁷ found a mean value of 27.30 volumes per cent, with extremes ranging from 22.09 to 33.54

Case 4 deserves special discussion In the first determination a high oxygen capacity was found (30 volumes per cent), if one considered the relatively high arterial saturation and oxygen pressure A month later the patient showed a much lower oxygen capacity (26.3 volumes), with only a small change in arterial oxygen saturation and pressure

37 Aste-Salazar, H., and Hurtado, A. The Affinity of Hemoglobin for Oxygen at Sea Level and at High Altitudes, *Am J Physiol* **142** 733, 1944

38 Meakins, J. C. Gases in Human Arterial Blood in Certain Pathological Pulmonary Conditions, and Their Treatment with Oxygen, *J Path & Bact* **24** 79, 1921

39 Campbell, J. M. H., Hunt, G. H., and Poulton, E. P. An Examination of the Blood Gases and Respiration in Disease, with Reference to the Cause of Breathlessness and Cyanosis, *J Path & Bact* **26** 234, 1923

40 Himwich, H. E., and Loebel, R. O. The Oxygen Saturation of Hemoglobin in the Arterial Blood of Exercising Patients, *J Clin Investigation* **5** 113, 1927

41 Kountz, W. B., Alexander, H. L., and Dowell, D. Emphysema Simulating Cardiac Decompensation, *J A M A* **93** 1369 (Nov. 2) 1929

42 Hurtado, A., Kaltreider, N. L., and McCann, W. S. Studies of Total Pulmonary Capacity and Its Subdivisions. IX. Relationship to the Oxygen Saturation and Carbon Dioxide Content of the Arterial Blood, *J Clin Investigation* **14** 94, 1935

43 Kaltreider, N. L., Hurtado, A., and Brooks, W. D. W. Study of the Blood in Chronic Respiratory Disease, with Special Reference to the Volume of the Blood, *J Clin Investigation* **13** 999, 1934

We believe that the patient had had a period of severe anoxemia, with a corresponding increase of the hemoglobin capacity, and had improved before being admitted to the service. When the determinations were carried out, the arterial saturation was higher but the hemoglobin capacity had not yet reached a new value in accordance with the improved oxygenation of the blood. In cases 17 and 18 the oxygen capacity was low, notwithstanding the severe anoxia, the patients in these cases were the only two females in our series.

In order to compare our data with those obtained by Hurtado, Merino and Delgado⁴⁴ at high altitude, our patients were classified into two groups, those with arterial saturation above 80 per cent and those with saturation below 80 per cent. In the Ayerza group with an arterial saturation of 86.4 ± 0.63 volumes per cent, a hemoglobin content of 18.82 ± 0.91 Gm per hundred cubic centimeters was obtained, as compared with 87.6 ± 0.27 and 18.82 ± 0.15 obtained by Hurtado and others in native residents at an altitude of 3,730 meters. In the group with lower saturation the figures were 74.7 ± 2.04 volumes per cent and 20.1 ± 0.17 Gm of hemoglobin for the Ayerza group and 81.4 ± 0.45 volumes per cent and 20.76 ± 0.20 Gm for the residents at 4,540 meters.

This shows that in patients with pulmonary disease a coarse correlation exists between the degree of the anoxia and the response of the bone marrow and that this response was less in our second group than in persons at high altitude. This difference may be explained by the finding of Hurtado and others⁴⁴ that when the arterial saturation reaches a value of about 60 to 70 per cent there is a decrease rather than a further increase in the hemoglobin content and the red blood cell count.

The question arises why in most cases of anoxemia due to pulmonary changes the polycythemic response tends to be less than when there are corresponding degrees of arterial oxygen unsaturation at high altitude, as pointed out by Hurtado and his co-workers. This may be due, in part at least, to the fact that in many pulmonary diseases the anoxic stimulus is variable, depending on the degree of the bronchial spasms, or to other factors.

We believe that these results support the view that the anoxic stimulation is the only cause of the increase in hemoglobin found in this disease.

Hematocrit Readings—To calculate the hemoglobin concentration per volume of red cells, hematocrit readings were made on the same sample of arterial blood in which the hemoglobin content was determined gasometrically. The results presented in table 6 are compared with those obtained in normal subjects at sea level or at high altitude and in patients with pulmonary fibrosis and emphysema. It can be seen that

44 Hurtado, A., Merino, C., and Delgado, E. Influence of Anoxemia on the Hemopoietic Activity, *Arch Int Med* 75:284 (May) 1945.

the hemoglobin content per hundred cubic centimeters of red cells is lower in our patients. The group at high altitude, in which the hemoglobin content of the blood is similar to that in our group, has an average hemoglobin concentration of 34.6 Gm per hundred cubic centimeters of cells, as compared with 29.3 in our cases. This difference is too great to be explained by the water shift produced by the increased

TABLE 6—*Values for Hematocrit, Hemoglobin and Hemoglobin to Hematocrit Ratio in Normal Persons at Sea Level and at High Altitude and in Patients with Pulmonary Disease*

A			
Case	Hematocrit, Volume, per Cent	Hemoglobin, Gm /100 Cc	Hemoglobin to Hematocrit, per Cent
2	61.9	18.52	30.4
4	70.4	22.10	31.4
	62.84	18.90	30.3
10	70.5	20.80	29.5
	66.8	19.84	29.7
12	67.7	20.15	29.8
13	70.1	19.6	28.0
15	69.9	20.1	28.8
	70.6	20.4	28.9
Mean	68.6	20.05	29.30
B			
Normal Persons at Sea Level			
Hurtado and others ⁴⁴	46.8	16	34.2
Kaltreider and others ⁴³	45.1	16.2	35.9
Haden, R. L. <i>Iolia haemat</i> 31 113, 1925	45	15.23	33.9
Altitude (4,540 M.)			
Hurtado and others ⁴⁴	59.9	20.76	34.6
Emphysema			
Kaltreider and others ⁴³	46.3	16.2	35.0
Fibrosis			
Kaltreider and others ⁴³	49.7	16.6	33.4
Ayerza's Syndrome			
Author's data	65.6	20.05	29.30

In table A are the individual values of some of our patients, and in table B our average value was compared with those reported in the literature for normal persons at sea level and at high altitude and for patients with emphysema and fibrosis.

carbon dioxide tension of the arterial blood in the patients at high altitude. It is possible that the slight acidosis present in our patients could impair the production of hemoglobin by the bone marrow. The results obtained in 3 patients with morbus caeruleus point in the same direction. In 2 of them, with a normal arterial (p_H)_s, the hemoglobin values per hundred cubic centimeters of red cells were 33.2 and 31.8, and in the other, with an arterial (p_H)_s of 7.30, values of 28.5 and 29.60 were secured. However, we realize that these results are far from con-

clusive and that other factors, such as poor general condition and infections, can be important

Oxygen Saturation and Content of the Arterial Blood—Table 7 shows that in our cases the average oxyhemoglobin content of arterial blood was 20.44 volumes per cent. The patients in cases 17 and 18 have been excluded because they were emphysematous anoxic women without polycythemia. The value is higher than that of 19.50 ± 0.16 found by Hurtado, Kaltreider and McCann⁴² in cases of pulmonary fibrosis and that of 18.75 ± 0.27 found by the same authors in cases of emphysema.

TABLE 7—*Characteristics of the Arterial and Equilibrated Blood of Patients with Pulmonary Disease*

Case	Arterial pO ₂ , Mm Hg	Arterial HbO ₂ , per Cent	Arterial HbO ₂ , Volumes per Cent	HbO ₂ Capacity, Volumes per Cent	Arterial pCO ₂ , Mm Hg	Arterial Total (CO ₂) _b , Volumes per Cent	(T40) _b *, Volumes per Cent	(T40) _s , Volumes per Cent	Arterial (pH) _s
1	50.0	85.4	22.24	26.04	52.0	52.60	45	57.2	7.33
2	44.5	79.9	20.73	25.96	64.8	63.89	51.0	64.6	7.32
3	57.5	87.5	21.75	24.84	53.0	50.12	43.1	53.7	7.30
4	53.0	87.4	26.23	30.00	49.0	51.30	44.5	57.9	7.36
	52.0	84.2	21.30	25.92	65.0	63.30	49.8	62.8	7.31
5	55.0	88.4	18.86	21.35	59.5	59.95	50.7	61.7	7.32
6	53.0	87.8	20.90	23.80	46.0	49.27	45.2	55.8	7.36
7	49.0	84.2	18.82	22.35	56.0	57.60	48.2	59.2	7.33
8	57.5	86.7	20.46	23.59	55.0	56.28	48.3	60.7	7.33
	50.5	81.4	18.74	23.00	62.0	64.65	62.9	66.3	7.34
9	45.0	81.2	18.70	22.90	56.0	62.00	52.6	65.2	7.37
10	45.2	77.3	21.56	27.87	52.0	53.10	45.1	57.7	7.34
	43.5	75.4	20.03	26.57	45.2	44.90	40.4	50.6	7.33
12	40.3	79.2	21.25	26.83	55.0	58.30	49.3	63.0	7.36
13	36.0	71.0	18.64	26.23	58.3	65.78	53.8	69.3	7.39
	44.5	80.0	21.60	27.00	63.6	62.10	49.0	63.0	7.32
15	37.0	66.4	17.86	26.90	70.0	65.10	49.2	63.2	7.29
	33.6	63.6	18.72	27.32	67.2	64.28	48.5	62.1	7.30
17	55.0	86.1	14.25	16.55	62.0	62.24	53.4	63.2	7.30
18	42.5	82.7	12.88	15.57	50.0	62.65	58.00	68.2	7.41
Mean	47.94	81.75	20.44 ± 0.47	25.07	56.61	57.7	48.17 ± 0.93	60.55 ± 1.22	7.33

* (T40)_b means total carbon dioxide content of the blood equilibrated at 40 mm. of mercury of carbon dioxide pressure and complete saturation. (T40)_s is the corresponding value in plasma or serum.

The differences are significant in both instances. In a recalculation of the data of Robinson⁸ on normal men between 40 and 60 years, an average value of 19 volumes of oxygen per cent in arterial blood was obtained. Dill, Edwards and Consolazio⁴⁵ found an average oxygen content of arterial blood of 19.15 volumes per cent in 12 normal men aged 23 to 45. These results show that in Ayerza's syndrome the

45 Dill, D. B., Edwards, H. T., and Consolazio, W. V. Blood as a Physico-chemical System. XI. Man at Rest, *J. Biol. Chem.* **118**: 635, 1937.

oxygen content of the arterial blood is slightly increased. They are in accordance with the findings of Berconsky, who in 8 cases of Ayerza's syndrome found a mean value of 21.15 volumes per cent of oxygen in arterial blood. A similar increase has been found at high altitude by Talbott and Dill⁴⁶ in healthy workmen living at 17,500 feet, with an average of 22.54 volumes per cent.

As found by all the workers in this field, the oxygen saturation was below the normal figure in all cases, the values ranging from 88.4 to 66.4 per cent. In healthy subjects between 40 and 60 years Robinson⁸ found an average saturation of 93 per cent, extreme values being 90 and 97 per cent. The recent work of Roughton and others⁴⁷ questioned the validity of the calculation of arterial oxygen saturation with the tonometer technic. However, since we have employed the same method as Robinson, both values can be compared. Moreover, if it is admitted that the oxyhemoglobin capacity obtained by this method is about 2 per cent too high, as calculated by Roughton and others,⁴⁷ our saturation values will be only about 1.5 per cent too low.

Arterial Oxygen Pressure—The oxygen pressure in the arterial blood was calculated from the oxygen dissociation curve and the arterial saturation. In cases in which no dissociation curve was made, arterial oxygen pressure was obtained with the use of a standard curve brought to the arterial p_H of the patient. As in most cases the arterial oxygen saturation was below 85 per cent, the error introduced by underestimating the saturation in the amount calculated by Roughton and others⁴⁷ is practically unimportant. In the remainder of the cases (86 to 88.4 per cent saturation) the estimated arterial oxygen pressure will be only about 3 to 4 mm. of mercury too low.

The results are summarized in table 7. It is shown that oxygen pressure was below the normal value in all cases.

Arterial Carbon Dioxide and p_H —The alkaline reserve ($T 40$)_b, defined as the volumes of carbon dioxide per hundred cubic centimeters of oxygenated blood at a carbon dioxide pressure of 40 mm. of mercury, was found to be within the normal range in almost every case (table 7). The average was 48.17 volumes, close to the values for normal persons reported in the literature, which include a mean of 48 volumes in the basal arterial blood of 12 men reported on by Dill, Edwards and Consolazio⁴⁸ and means ranging from 47.2 to 49.4 volumes reported by Robinson⁸ in healthy subjects from 25 to 80 years old. The average

46 Talbott, J. H., and Dill, D. B. Clinical Observations at High Altitude. Observations on Six Healthy Persons Living at 17,500 Feet and Report of One Case of Chronic Mountain Sickness, *Am J M Sc* **192** 626, 1936.

47 Roughton, F. J. W., Darling, R. C., and Root, W. S. Factors Affecting the Determination of Oxygen Capacity Content and Pressure in Human Arterial Blood, *Am J Physiol* **142** 708, 1944.

alkaline reserve of the plasma, $(T40)_s$,⁴⁸ was 60.55 volumes of oxygen per cent, higher than the value of 58 volumes found by Dill, Edwards and Consolazio.⁴⁵ The alkaline reserve is increased in plasma but not in whole blood because of the fact that the increased red cell volume (in which the carbon dioxide content is lower than in the plasma) decreases the carbon dioxide content of the total blood.

In case 12 four points on the carbon dioxide dissociation curve of arterial blood at 37 C and complete saturation were determined. The curve was steeper than that in normal persons because of the high hemoglobin content of the blood, but it was in agreement with that calculated according to the nomogram of Henderson and others¹ from the alkaline reserve and the hemoglobin capacity. As Henderson's nomogram has been constructed from data obtained on normal persons, the results suggest that no change in the oxyhemoglobin base-binding properties has occurred.

The mean value of total carbon dioxide content of the arterial blood, $(TCO_2)_a$, was 57.7 volumes per cent, higher than the means varying from 49.2 to 51.6 volumes found by Robinson⁸ in his adult groups, that of 48.6 found by Dill, Edwards and Consolazio⁴⁵ in 12 normal men studied under basal conditions and that of 49.9 found by Looney and Jellinek⁴⁹ in 25 normal male subjects. This increase in $(TCO_2)_a$ of the arterial blood confirms the results obtained by Berconsky (1933) in cases of Ayerza's syndrome.

Scott,²⁶ Meakins and Davies¹² and Dautrebande⁵⁰ found that in emphysema there is an increase in the carbon dioxide content of the arterial blood and Hurtado, Kaltreider and McCann⁴² that the carbon dioxide content of arterial blood was increased chiefly in cases of emphysema but not in cases of pulmonary fibrosis.

The carbon dioxide pressure of the arterial blood has been calculated as explained under "Methods." Our mean value of 56.6 mm of mercury is higher than the 43 mm obtained by Robinson in healthy adults aged between 40 and 60 and the 41 mm obtained by Dill, Edwards and Consolazio⁴⁵ in younger subjects. In our series, the values in all cases but 3 are over 50 mm, which can be taken as the upper normal limit for subjects of the same age, according to Robinson's data.⁸ When the carbon dioxide pressure of arterial blood was compared with its oxygen

48 The carbon dioxide content of the plasma was calculated from $(T40)_s$ and the hemoglobin capacity with the cartesian nomogram of Henderson and others.¹

49 Looney, J. M., and Jellinek, E. M. The Oxygen and Carbon Dioxide Content of the Arterial and Venous Blood of Normal Subjects. *Am J Physiol* 118: 225, 1937.

50 Dautrebande, L. L'équilibre acide-base chez les emphysemateux. Ses variations au cours de la décompensation cardiaque, *Compt rend Soc de biol* 93: 1025, 1925.

pressure or hemoglobin saturation, a poor correlation was found. However, the patients with highest arterial carbon dioxide pressure were those in whom oxygen saturation reached its lowest values.

The p_H of arterial serum ranged from 7.29 to 7.39, with an average value of 7.33, lower than the means of 7.37 to 7.42 found by Robinson in the various age groups. The lowest occurred in men between 48 and 55, 7.33 and 7.45 being the extreme values in the whole series of his subjects. These values compare closely with those obtained by others, i.e., Mori,⁵¹ 7.40 to 7.42 in the various decades between the ages of 15 to 68, Shock and Hastings,⁵² 7.40 in capillary blood in 39 normal men, and Dill, Edwards and Consolazio,⁴⁵ 7.40 in arterial blood of 12 normal men under basal conditions (range, 7.35 to 7.44).

From the previous data the conclusion can be drawn that primary carbon dioxide excess exists in the presence of chronic pulmonary insufficiency, partially compensated by the increase in the plasma bicarbonates.

TABLE 8—*Distribution of Water, Combined Carbon Dioxide, Chloride and Hydrogen in Oxygenated Blood*

Case	(H ₂ O) _s , Gm/Cc	(H ₂ O) _c , Gm/Cc	(Cl) _s , mEq	(Cl) _c , mEq	rCl	(BHCO ₃) _s , mEq	(BHCO ₃) _c , mEq	rHCO ₃	(pH) _s	(pH) _c	rH
2	0.930	0.740				29.01	19.35	0.839	7.39	7.21	0.53
10	0.932	0.742				25.31	16.98	0.842	7.40	7.22	0.53
15	0.926	0.745	99.3	51.9	0.650	30.01	18.53	0.768	7.41	7.19	0.48

Arterial blood was equilibrated in a tonometer at a pO_2 of 100 mm of mercury and to a pCO_2 necessary to get a pH close to 7.40.

Distribution of Water and Electrolytes in Serum and Cells—In 3 of the most severe cases, water, bicarbonate, p_H and chlorides were determined in red cells and plasma. The results are summarized in table 8.

Water content per liter of red cells (H₂O)_c ranged between 740 and 745, compared with the mean value of 720, extremes being 714 and 732, obtained in 12 healthy men by Dill, Edwards and Consolazio.⁴⁵ Water serum values (H₂O)_s ranged between 926 and 932, compared with the mean value of 938, with a range of 936 to 941, obtained by Dill and others. Notwithstanding the small number of our cases, we believe that on account of the slight dispersion of the values and the lack of

51 Mori, Z. Age and Muscular Exercise, Jap J M Sc, III, Biophysics 3:309, 1936, cited by Robinson.⁸

52 Shock, N. W., and Hastings, A. B. Studies of the Acid-Base Balance of the Blood. III. Variation in Acid-Base Balance of the Blood in Normal Individuals. J Biol Chem 104:585, 1934.

overlapping the differences found can be considered significant. The higher water content of the red cells keeps pace with the finding, mentioned previously, that the hemoglobin content per volume of red cells is diminished in these patients.

The bicarbonates in the cells and serum were increased, and their distribution in the fully oxygenated arterial blood at p_H 7.40 fell within the values given by Dill and others for normal persons.

As expected, the chlorides in the serum and cells were diminished in the only determination made, the distribution being near the normal value.

The distribution of hydrogen was about 0.50, lower than the averages found in smoothed curve of Dill and others.⁴⁵

Hemorespiratory Exchanges—In table 9 the oxygen and carbon dioxide pressures of arterial blood have been compared with the corresponding pressures in alveolar air. It can be seen that the arterial oxygen pressure is in every case lower than the alveolar one, differences ranging from 10.3 to 53.8, with an average of 30.7 mm of mercury. In resting normal subjects at sea level the alveolar oxygen difference, ΔpO_2 , estimated with the same method as we have employed, is about 20 mm of mercury. However, Roughton and others⁴⁷ have shown that this difference is produced by systematic error in the calculation of the arterial oxygen pressure and that a nearly perfect equilibrium between alveolar and arterial gases does exist in normal subjects. Nevertheless when the saturation of arterial blood is below 85 per cent, the form of the oxygen dissociation curve makes the error in the calculation of the arterial oxygen pressure negligible and consequently difference in alveolar oxygen pressure practically disappears. For that reason, we will compare the values for alveolar oxygen difference in our patients with those obtained with the same method in healthy men at high altitude having a similar oxygen saturation.

At an altitude of 4,700 meters, with a mean arterial oxyhemoglobin of 78 per cent, Dill, Christensen and Edwards⁵³ found an average alveolar oxygen difference of +3.4 mm of mercury, extreme values being +8.2 and -1.3. If one considered 8.2 the upper normal limit alveolar oxygen difference was increased in all our patients.

The alveolar carbon dioxide difference in healthy subjects aged 40 to 60 years was found to be about +2 mm of mercury by Robinson, extreme values ranging from -5 to +7 mm. In our cases (table 9) the mean alveolar carbon dioxide difference was +3.4 mm, values ranging from -14.4 to +13.1, indicating a small increase in carbon dioxide pressure but a greater scattering of the values.

⁵³ Dill, D. B., Christensen, E. H., and Edwards, H. T. Gas Equilibria in the Lungs at High Altitudes, *Am J Physiol* **115**: 530, 1936.

In discussing the mechanism by which the differences between the alveolar and arterial blood gases are produced, several possibilities must be considered

A Impairment of Gas Diffusion Through the Alveolar Wall The fact that alveolar carbon dioxide difference is smaller than alveolar oxygen difference favors the hypothesis that an impairment in the alveolar permeability may exist, this being so, the former could be calculated from the latter. However, the considerable spread of the figures for alveolar carbon dioxide difference prevents closer analysis. On the other hand, the mathematical analysis of the diffusion of gases through the lung does not support the hypothesis previously mentioned

TABLE 9—*Relation Between Arterial and Alveolar Carbon Dioxide and Oxygen Pressure in Patients with Emphysema and Fibrosis of the Lung*

Case	pO ₂ in Millimeters of Mercury			pCO ₂ in Millimeters of Mercury		
	Alveolar	Arterial	Difference*	Alveolar	Arterial	Difference
2	63.0	45.6	17.4	62.1	72.0	— 9.9
	61.1	44.5	16.6	63.8	64.8	— 1.0
3	98.5	57.5	41.0	38.6	53.0	—14.4
4	92.5	53.0	39.5	46.8	49.0	— 2.2
6	95.5	53.0	42.5	41.4	46.0	— 4.6
7	60.6	49.0	11.6	63.6	56.0	+ 7.6
8	67.8	57.5	10.3	63.9	55.0	+ 8.9
	72.6	50.5	22.1	61.4	62.0	— 0.6
10	91.0	45.2	45.8	40.8	52.0	—11.2
	97.0	43.5	53.5	38.2	45.2	— 7.0
12	78.7	40.3	38.4	49.3	55.0	— 6.3
13	87.9	35.0	52.9	47.9	58.3	—10.4
	65.0	44.5	20.5	63.6	63.6	0
15	71.2	38.6	32.6	61.6	67.2	— 5.6
17	82.2	55.0	27.2	50.0	62.0	—12.0
18	62.8	42.5	20.3	63.1	50.0	+13.1
Mean	77.95	47.20	30.75	53.50	56.91	— 3.44

* The difference was calculated by subtracting the values for the pressure of the gases in the arterial blood from the corresponding values in the alveolar air

The amount of oxygen diffusing through the lung in a given time can be obtained by the following expression $O_2 = K \int_0^t (P_a - P_b) dt$ in which

O_2 indicates amount of oxygen diffusing, K diffusion constant and P_a and P_b alveolar and blood oxygen pressure. The alveolar oxygen pressure can be considered as constant, but the oxygen pressure of the blood changes from venous to arterial. In order to integrate $(P_a - P_b)$, $P_b(f)t$ must be known, but as a first approximation the mean values between alveolar and arterial pressure can be used. If venous oxygen pressure is taken to be 20 mm of mercury and arterial oxygen pressure 47 mm, the mean will be 35.5 mm and $(P_a - P_b)$ will be $78 - 33.5$, or 44.5 mm

If the differences between alveolar and arterial gases depend on generalized impairment of the diffusion process, 44.5 mm of mercury has to be considered as a diffusion gradient, then

$$O_2 = K (44.5)$$

As the data were obtained on patients at rest, the basal oxygen consumption, for example, 250 cc, has to be transferred through the lung with a head of pressure of 44.5 mm of mercury

In order to increase the oxygen diffusion, K being constant, a corresponding increase in the diffusion gradient must occur, for instance, if 250 cc of oxygen per minute passes through the lung with a head of pressure of 44.5 mm of mercury for passing 500 cc per minute, a head of pressure of 89 mm of mercury needs to be postulated. Since this figure is higher than the average alveolar oxygen pressure, the results will indicate that most of these patients could not duplicate their basal metabolic rate, even when blood oxygen pressure would be zero. Although we did not study our patients under exercise, the data of Kaltreider and McCann⁵⁴ obtained on patients with considerable emphysema indicate that during exercise the oxygen consumption was about 700 to 800 cc per minute and the arterial oxygen saturation did not fall below 85 per cent. This makes it problematic that alveolar oxygen difference can be due to a generalized diffusion impairment. Krogh,⁵⁵ studying the diffusion coefficients in cases of emphysema with the use of the carbon monoxide method, was unable to detect significant differences in normal persons. Further evidence against considering alveolar oxygen difference as a diffusion gradient will be presented later.

B Uneven Distribution of the Gases in the Lungs Under "Alveolar Air" evidence has been presented for uneven distribution of the gases in the lungs. In order to compare arterial and alveolar pressures, alveolar samples taken four seconds after the beginning of the expiration were used, in some cases better concordance could be found with subsequent samples. It is possible that in most cases the residual air may have a lower oxygen and a higher carbon dioxide content than what we accepted as the "alveolar sample." If the "alveolar sample" averaged the composition of the most and least ventilated alveoli, alveolar carbon dioxide pressure will coincide with arterial carbon dioxide pressure because of the almost rectilinear form of the carbon dioxide dissociation curve. On the contrary, because of the shape of the oxyhemoglobin dissociation curve, the blood that passes through the hyperventilated alveoli cannot increase much more its oxygen content and the oxygen pressure in the mixed arterial blood will remain lower than that of mixed alveolar air.

54 Kaltreider, N. L., and McCann, W. S. Respiratory Response During Exercise in Pulmonary Fibrosis and Emphysema, *J. Clin. Investigation* **16** 23, 1937.

55 Krogh, M. The Diffusion of Gases Through the Lungs of Man, *J. Physiol.* **49** 271, 1915.

C Stratification of the Air in the Alveoli Beitzke⁵⁶ has suggested an explanation on the basis of the imperfect mixing of gases within the alveoli According to him, dilatation of the opening of the alveolar duct into the atrium will produce stratification of the gas, equilibrium being reached between the blood and the gas layer near to the alveolar wall but not between the blood and the more distant layers Nevertheless, Christie¹³ has analyzed this hypothesis and concluded that it cannot be maintained

D Arteriovenous Shunt If blood is shunted through the lung without making contact with an (fibrotic or hepatized zones maintaining the circulation and the arterial changes) alveolar oxygen difference will increase markedly and alveolar carbon dioxide difference only slightly, as will be discussed in the second paper of this series

It would be possible to differentiate the four conditions by giving the subject pure oxygen to breathe and comparing the oxygen pressure in alveolar air with that of arterial blood

1 If alveolar oxygen difference is a diffusion gradient, oxygen breathing would diminish it and the value reached after the mixing in the lung is completed (about ten minutes) would be maintained during the period of oxygen administration (For further discussion see Fasciolo and Chiodi⁵⁷)

2 If caused by uneven ventilation, alveolar oxygen difference first would increase but later, when nitrogen has been washed out, would decrease

3 If due to stratification of the gas within the alveoli, alveolar oxygen difference would increase, with no changes in time Hyperventilation, however, is apt to reduce the increase

4 If there exists an auriculoventricular shunt, alveolar oxygen difference would show a great increase, with no changes because of time or hyperventilation

Although we did not investigate these points systematically, our results (see following paragraphs) do not support the view that an impairment of gas diffusion needs to be postulated as an explanation of the increased oxygen pressure found in these patients

Effect of Breathing Pure Oxygen—On Respiration Table 10 shows the effect of breathing pure oxygen on the pulmonary ventilation in our group In all cases, with the exception of case 10, the ventilation decreased while the patients were breathing oxygen, differences ranging from 100 to 1,390 cc The respiratory frequency (table 11) either did

56 Beitzke, H Zur Mechanik des Gaswechsels beim Lungenemphysem, Deutsches Arch f klin Med **46** 91, 1925

57 Fasciolo, J C, and Chiodi, H Arterial Oxygen Pressure During Pure O₂ Breathing, Am J Physiol **147** 54, 1946

not change or was slightly decreased, with a tendency toward a decrease of the tidal air. Calculated as a percentage of the ventilation in air, the diminution (case 10 excepted) ranged from 6.34 to 26.5 per cent (table 10). The decrease of ventilation produced by oxygen has been observed by Ayeiza, Solari and Berconsky,¹⁴ Berconsky¹⁷ and Capdehouat.¹⁵ No significant correlation could be drawn between the depressor effect of oxygen and arterial carbon dioxide pressure, oxygen pressure, or the carbon dioxide effect on breathing.

TABLE 10—*Effect of Oxygen and Carbon Dioxide on Ventilation in Patients with Pulmonary Disease**

Case	Lung Ventilation, Liters per Minute				Effect of CO ₂ in Air and in Oxygen, Liters per Minute	Ventilation While Breathing Oxygen and While Breathing Air, Liters per Minute	Increase by 4% CO ₂ in Air, %	Ventilation While Breathing Oxygen and While Breathing Air, %
	Breathing Air	Breathing Air Plus 4% CO ₂	Breathing Pure Oxygen	Breathing Pure Oxygen Plus 4% CO ₂				
2	6.65	8.30	5.69			-0.96	29.8	-14.4
3	8.37	12.51	7.05	12.90	-1.71	-1.32	49.5	-15.8
4	7.00	10.72	6.48	9.26	+0.94	-0.52	53.2	-7.4
	6.96	11.11	5.78	8.41	+1.52	-1.18	60.0	-17.0
5	6.00		4.41			-1.59		-26.5
6	9.04	16.55	8.04	15.01	+0.54	-1.00	83.0	-11.1
7	7.72	14.46	7.23	13.21	+0.76	-0.49	87.4	-6.2
8	6.48	9.62	6.38	7.02	+1.50	-0.10	48.5	-1.5
	4.92	7.09	4.59	7.56	-0.80	-0.33	44.4	-6.7
10	9.63	17.08	10.61	17.84	+0.22	+0.98	100.0	+10.2
							77.5	
13	7.54	11.28	6.54	9.61	+0.57	-1.00	51.5	-13.3
15	8.20	10.95	6.81	9.23	+0.33	-1.39	33.6	-16.6
	8.38	10.22	7.17	9.83	-0.82	-1.21	22.0	-14.4
17	5.34	6.75	4.79	6.34	-0.14	-0.55	26.4	-10.3

* Values are expressed in liters per minute at 37°C and at the prevailing barometric pressure. The values of column 6, effect of CO₂ in air and in oxygen, were calculated by subtracting from the figures for ventilation during the breathing of 4 per cent carbon dioxide in air or in oxygen the values obtained when the subject was breathing air or oxygen respectively. In the last two columns the effects of carbon dioxide and oxygen on ventilation are expressed as percentages of the pulmonary ventilation when air was breathed.

On the Blood Oxygen Capacity. In 5 cases arterial blood was drawn before and during the seventeen to thirty minute period of oxygen breathing and its oxygen-combining capacity determined by the tonometric technic. It was decreased in 4 of the cases, ranging from 0.25 to 0.71 volume per cent. In 1 case an increase of 0.40 volume per cent was observed.

These results are in accord with those of Anthony,⁵⁸ who found a reduction of the hemoglobin and the red cell count in normal subjects breathing pure oxygen during fifteen to twenty minutes.

58 Anthony, A. J. Der Einfluss kurzdauernder Sauerstoffatmung auf Hämoglobingehalt und Erythrocytenzahl des menschlichen Blutes, *Ztschr. f. d. ges. exper. Med.* 105: 417, 1939.

On Oxygen Pressure The changes in the composition of arterial blood produced by breathing pure oxygen during seventeen to thirty minutes are summarized in table 12. The dissolved oxygen was calculated by subtracting from the total oxygen content of the arterial blood the oxygen-combining capacity as found by equilibrating a sample of the same blood in a tonometer, and from this figure arterial oxygen pressure was calculated with the use of the oxygen solubility coefficient. Although the values calculated by this method are too low (Fasciolo and Chiodi⁵⁷), it is safe to compare the mean value in the Ayerza group with the one

TABLE 11—*Effect of Oxygen and Carbon Dioxide on the Tidal Air and Respiratory Rate in Patients with Pulmonary Disease**

Case	Tidal Air, Liters					Respiratory Rate, per Min				
	Air	O ₂	O ₂ — Air	4% CO ₂	4% CO ₂ —Air	Air	O ₂	O ₂ — Air	4% CO ₂	4% CO ₂ —Air
2	0.37	0.38	+0.01	0.48	0.11	19	16	—3	18	—1
	0.39	0.35	—0.04	0.49	0.10	16	16	0	16	0
	0.40	0.37	—0.03	0.58	0.18	16	14	—2	14	—2
3	0.69	0.58	—0.11	0.89	0.20	12	12	0	14	+2
4	0.43	0.53	+0.10	0.76	0.33	16	12	—4	14	+2
	0.38	0.36	—0.02	0.61	0.23	18	16	—2	18	0
5	0.74	0.73	—0.01			8	6	—2		
6	0.53	0.50	—0.03	0.82	0.29	17	16	—1	20	+3
7	0.59	0.60	+0.01	0.90	0.31	13	12	—1	16	+3
8	0.64	0.63	—0.01	0.80	0.16	10	10	0	12	+2
	0.41	0.38	—0.03	0.54	0.13	12	12	0	13	+1
10	0.50	0.64	+0.14	0.95	0.45					
	0.58	0.64	+0.06	1.10	0.52					
	0.80	0.96	+0.16	1.08	0.28					
13	0.46	0.37	—0.09							
	0.47	0.43	—0.04			18	18	0		
15	0.29	0.27	—0.02	0.39	0.10	28	25	—3	28	0
	0.29	0.29	0.00	0.36	0.07	28	24	—4	28	0
17	0.26	0.23	—0.03	0.32	0.06	20	20	0	21	+1

* Volumes reduced at 37 C and the prevailing barometric pressure

obtained in a series of healthy persons. In 8 normal subjects the average value of arterial oxygen pressure was 543 ± 26 mm of mercury, and in the patient group a mean value of 294 ± 40 mm was obtained, the difference of 249 ± 48 is highly significant. This brought about a great increase of alveolar oxygen difference in the patient group, which, as pointed out before, must be considered evidence against the existence of generalized impairment in the diffusion of oxygen through the alveolar wall. Arterial carbon dioxide pressure rose in all the patients during oxygen breathing, this is due to the fact that the ventilation is depressed by the oxygen and therefore alveolar carbon dioxide pressure increases. In case 10, however, this explanation does not hold, as oxygen produced hyperventilation. It is possible that the arterial puncture had

produced pain and modification of the breath, causing carbon dioxide retention. Arterial p_H was found to be diminished in every case during oxygen breathing with the exception of case 10. This effect is due to two factors: (a) increased carbon dioxide tension and (b) increased oxygenation of arterial blood, with the corresponding changes of hemoglobin in the more acid oxyhemoglobin.

The effect of inhalation of oxygen on ventilation shows that in these patients the anoxemia stimulates respiration and that when the stimulus is withheld ventilation decreases. According to our present knowledge, the anoxic stimulation of breathing is produced through the carotid and aortic bodies. Therefore our results suggest that the chemoreceptor system is active in these patients.

TABLE 12—*Changes Produced by the Breathing of Pure Oxygen in the Arterial Blood of Pulmonary Patients with Anoxemia*

Case	Ventilation, Liters per Minute			Arterial pCO_2 , Mm Hg			Arterial pO_2 , Mm Hg		Arterial p_H		
	Air	O ₂	Difference*	Air	O ₂	Difference	Air	O ₂	Air	O ₂	Difference
2	6.65	5.69	-0.96	64.8	73.0	+ 8.2	44.5	233	7.32	7.28	-0.04
4	7.04	6.32	-0.72	49.0	52.0	+ 3.0	53.0	516	7.36	7.34	-0.02
5	6.00	4.41	-1.59	59.5	71.0	+11.5	55.0	310	7.32	7.27	-0.05
7	7.72	7.23	-0.49	56.0	57.0	+ 1.0	49.0	326	7.33	7.32	-0.01
8	5.66	5.21	-0.45	62.0	72.0	+10.0	50.5	322	7.34	7.29	-0.05
10	9.1	10.34	+1.24	45.2	46.2	+ 1.0	43.5	229	7.33	7.33	0.00
13	7.32	6.19	-1.13	63.6	79.0	+15.4	44.5	162	7.32	7.24	-0.08
15	7.94	6.83	-1.11	67.2	78.2	+11.0	38.6	255	7.30	7.25	-0.05
Mean			-0.65			+ 7.6					-0.04

* The differences in the three columns were calculated by subtracting the values for air from the values for oxygen.

The effect of anoxemia on breathing could be explained in the following ways:

A The anoxemia, acting through the carotid body, makes the respiratory center more sensitive to carbon dioxide and/or p_H . In this case carbon dioxide or p_H or both are still the respiratory stimulus, but the threshold has changed.

B The low oxygen tension stimulates the respiratory center (via the carotid body) independently of carbon dioxide or p_H .

C There should be a summation of the stimulus of the carbon dioxide and the oxygen on the respiratory center. The stimulus of both gases would be independent and proportional to their concentration in the blood.

In figure 1 the effect of breathing pure oxygen on the arterial blood of these patients has been represented. If "A" is admitted as the mech-

anism of the hypoxemic stimulation, the increase in the carbon dioxide pressure or the p_H decrease during the breathing of oxygen will be a measure of the degree of the potentiation of the respiratory center. If "B" or "C" is the mechanism, differences should be looked on as the increase in carbon dioxide or hydrogen concentration necessary to reach the threshold of the respiratory center and to regain the whole control of breathing.

Besides these changes, the heart rate slowed down during the oxygen inhalation, showing an average decrease of about seven beats per minute. This is in accord with the findings of Whitehorn and others⁵⁹ in normal subjects.

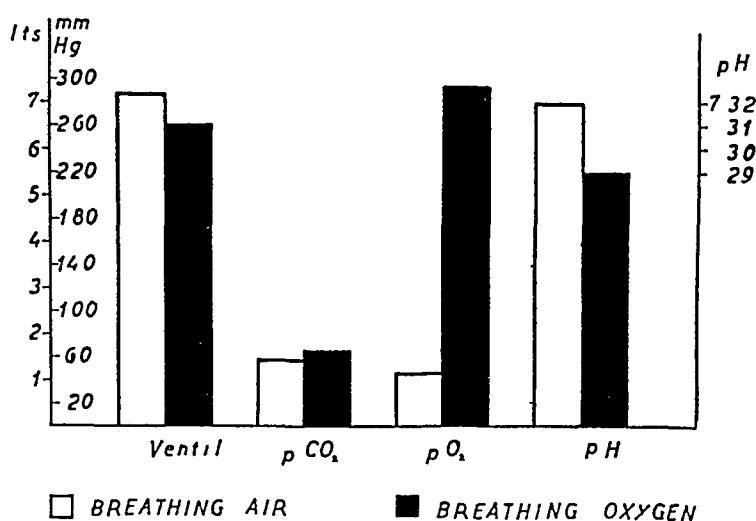


Fig 1—Effect of breathing pure oxygen on pulmonary ventilation, carbon dioxide pressure, oxygen pressure and p_H of the arterial blood in patients with pulmonary anoxia.

Effect of Carbon Dioxide on Breathing—The effect of breathing 4 per cent carbon dioxide on ventilation, summarized in table 10, was an increase of 54 per cent over the ventilation as measured when the subjects were breathing air.

Shock and Soley⁶⁰ with a similar technic showed that the respiratory volume is doubled in healthy subjects breathing 4 per cent carbon dioxide in air. Our observations, as those of Scott²⁶ and Meakins and Davies¹² in patients with emphysema, show that for a given amount of carbon dioxide there is a smaller increase in the ventilation in these patients than in normal persons.

59 Whitehorn, W. V., Edelmann, A., and Hitchcock, F. A. The Cardiovascular Responses to the Breathing of One Hundred Per Cent Oxygen at Normal Barometric Pressure, *Am J Physiol* **146** 61, 1946.

60 Shock, N. W., and Soley, M. H. Effect of Oxygen Tension of Inspired Air on the Respiratory Response of Normal Subjects to Carbon Dioxide, *Am J Physiol* **130** 777, 1940.

The increased ventilation is due to a deeper breathing, since respiratory rate showed only a small change. The heart rate was not significantly modified by carbon dioxide.

There is some correlation between the effect of carbon dioxide on ventilation and arterial carbon dioxide pressure, p_H and T40, which will be considered in the last paper of this series.

In order to decide if the anoxic stimulus potentiated the respiratory center to carbon dioxide, the effect of 4 per cent carbon dioxide in air (anoxic stimulus present) was compared with that of 4 per cent carbon dioxide in oxygen (anoxic stimulus withheld). In table 10, under column 6 are the results of subtracting the increase in ventilation from breathing 4 per cent carbon dioxide in oxygen from the increase produced by 4 per cent carbon dioxide in the air. If anoxemia had produced a potentiation of the respiratory center, the effect of carbon dioxide in air should be greater than that of carbon dioxide in oxygen.

TABLE 13—*Venous Pressure and Circulation Time*

Case	Venous Pressure, Mm H ₂ O	"Decholin" Circulation Time, Seconds	Ether Circulation Time, Seconds
2	120		10
3	134	22	8
4	135	18	9
6	100	28	10
8	95	20	14
9	65	26	
10	95		18
11	180		10
12	210		
13	130	29	15
14	270	23	11
15	310	32	20
17	120	19	11

Our results show that potentiation of the center was found to exist in 8 of 12 cases. In the remaining 4 the effect of carbon dioxide in air was less.

Although these findings do not permit us to draw conclusions they suggest that at least in some cases anoxia can make the respiratory center more sensitive to carbon dioxide.

Circulation—Venous Pressure (Table 13). Only 4 of 13 patients had elevated venous pressure (cases 11, 12, 14 and 15), and each of them had cardiac failure. The values in the remaining patients were within normal range whether or not they had cardiac insufficiency.

Weiss and Blumgart⁶¹ found normal values in practically all their emphysematous patients. On the contrary, Kountz and Alexander⁶² stated that the most constant circulatory finding in emphysema is an increased venous pressure. The discrepancies may be explained by differences in the measurement technics and the degree of emphysema and probably by the presence and the degree of cardiac failure.

Our results suggest that in pulmonary fibrosis and emphysema frankly elevated venous pressure is found only when cardiac insufficiency is superimposed. This is in agreement with the statements of Oppenheimer and Hitzig⁶³ and Kaltreider⁶⁴.

Circulation Time (Table 13) "Decholin" circulation time was prolonged in most of the subjects. In 2 cases the values were below twenty seconds. Ether circulation time was increased in all the cases but 1, in which it was found to be in the upper normal range.

The increased circulation times with both methods were found in patients with the most severe degree of heart failure.

No evident correlation between venous pressure and circulation time was observed.

Different results are reported in the literature. Weiss and Blumgart,⁶¹ working with radium C, found the arm to arm and pulmonary circulation times to be within normal limits in 21 of 25 emphysematous patients. As a matter of fact, some of these patients showed an increase in the velocity of the blood. Oppenheimer and Hitzig⁶³ found normal circulation times in patients with uncomplicated pulmonary emphysema, fast normal circulation times in some with a notable degree of cyanosis and polycythemia and prolonged circulation times only in the presence of frank myocardial failure. On the other hand, our results indicate that severe pulmonary emphysema and fibrosis with pronounced polycythemia result in prolonged circulation times even when there is no heart failure.

Blood Volume—Determinations of blood volume were made on 10 patients who had Ayerza's syndrome with different degrees of anoxemia. Six of the patients had good circulatory function when determinations were made, the remaining 4 having failure of the right side of the heart.

The results obtained are found in table 14. Total blood volume ranged between 5.21 and 11.95 liters, which corresponds to 72.4 to 163.7 cc per kilogram of body weight. These figures fall within

61 Weiss, S., and Blumgart, H. L. Studies on the Velocity of Blood Flow. VIII. The Velocity of Blood Flow and Its Relation to Other Aspects of the Circulation in Patients with Pulmonary Emphysema, *J Clin Investigation* **4** 555, 1927.

62 Kountz, W. B., and Alexander, H. L. Emphysema, *Medicine* **13** 251, 1934.

63 Oppenheimer, B. S., and Hitzig, W. M. The Use of Circulatory Measurements in Evaluating Pulmonary and Cardiac Factors in Chronic Lung Disorders, *Am Heart J* **12** 257, 1936.

64 Kaltreider, N. L. Differentiation Between Pulmonary and Cardiac Insufficiency in Chronic Pulmonary Disease, *Internat Clin* **4** 221, 1938.

TABLE 14—*Blood Volume*¹

Case	Plasma Volume, Liters	Hemato crit, per Cent Red Cells	Blood Volume and Body Weight		Plasma Volume and Body Weight		Red Cell Volume and Body Weight		Blood Volume and Body Surface		O ₂ Capac ity, Volumes, per Cent	O ₂ Satura tion, per Cent	Venous Pres sure, Mm. H ₂ O*	Circulation Time*		
			Red Cell Volume, Liters	C _c /Kg	Variation, per Cent	C _c /Kg	Body Weight	C _c /Kg	Body Weight	L/Sq M					Variation per Cent	
2	2.28	60.2	2.93	5.21	74.8	— 1	32.7	—18	42.1	+ 24	3.30	+12.5	25.21	79.4	120	10
3	3.08	51	3.21	6.30	72.4	— 2	35.5	—12	36.9	+ 9	3.60	+26	24.84	87.5	124	8
4	2.14	71	5.25	7.39	112.0	+ 51	32.5	—19	79.5	+134	4.40	+50	30.0	87.4	135	9
6	2.82	52.7	3.15	5.97	82.9	+ 12	39.2	— 2	43.7	+ 29	3.58	+22	23.80	87.8	100	10
7	2.95	61	4.42	7.37	84.7	+ 14	33.9	—16	50.8	+ 50	4.10	+40	22.35	84.2		28
8	2.65	60	3.98	6.64	132.8	+ 79	53.1	+32	79.7	+135	4.23	+44	23.0	81.4	95	14
10	2.28	72	5.85	8.13	141.3	+ 91	39.6	— 1	101.7	+200	4.87	+66	27.87	77.3	95	18
13	2.50	70.1	5.84	8.34	146.4	+ 94	43.9	+ 9	102.5	+202	4.74	+61.5	26.23	71.0	110	19
14	3.00	67.9	6.35	9.35	112.6	+ 51	36.1	—10	76.5	+126	5.53	+89			100	9
15	2.92	75.5	9.02	11.95	163.7	+121	40.1	0	123.6	+263	7.12	+142	27.3	68.6	160	19
Mean	2.66	64.1	5.00	7.66	112.4	+ 47.7	38.66	— 3.9	73.7	+115.4	4.56	+55.3	25.62	80.5	115.4	13

* Measured at the moment of the determination of blood volume

our normal standard range (\bar{x}) in 2 of the 10 cases and over it in the other 8. The increase in blood volume according to weight varied from 12 to 121 per cent. Since some of the patients had heart failure, with considerable edema, the blood volume in each patient was compared with our standard values according to meters of height. Accordingly, all the patients showed an increase in blood volume which ranged between 12.5 and 142 per cent, with a mean increase of 55.3 per cent in the whole group.

Plasma volume ranged between 2.28 and 3.08 liters, or 32.5 to 53.1 cc per kilogram of body weight. In 3 patients the plasma volume per kilogram was within normal limits, in 5 there was a decrease which ranged between 10 and 19 per cent, and in 2 there was an increase of 9 and 32 per cent respectively. The average variation in the whole group was -3.9 per cent.

Red cell volume varied from 2,935 to 9,025 cc, which gives a range between 36.9 and 123.6 cc per kilogram. These figures are all above our normal mean standard values. The increase in the 10 cases varied from 9 to 234.1 per cent.

The results show that in Ayeiza's syndrome there is an increase in the total blood volume which is mostly due to the increase in the red blood cells. Plasma volume did not change much in patients with chronic pulmonary disease. The deviation from normal of more than 10 per cent found for some patients according to weight can be explained by the fact that they were in cardiac failure with considerable edema, which leads to underestimation of the plasma volume per kilogram and/or undertreatment with mercurial diuretics. On the other hand, the only patient in whom plasma volume per kilogram was definitely increased was undernourished, and, as is known, this condition leads to overestimation of the plasma volume per kilogram.

Stimulation of the medulla by anoxemia appears to be the most important cause of the production of hypervolemia in Ayeiza's disease. As has been previously mentioned, this anoxemia depends on hypoventilation of the lungs due to emphysema and fibrosis. Even though the higher blood volumes were obtained in patients with the higher degree of anoxemia, no good correlation could be found between arterial oxygen saturation and blood volume when ungrouped data were considered. On the other hand, when three groups of patients were distinguished according to the degree of arterial oxygen saturation, a definite correlation between these two factors was found (fig. 2).

Actually we are not able to explain the difference found in the reaction of patients with similar degrees of anoxemia. It is possible that some of these differences can be explained, as in case 4, on the basis that examination is performed shortly after a change in the arterial saturation has occurred and before the blood volume is given a chance to become equilibrated with it. However, we must admit also an individ-

ual response of the medulla to anoxemia, since even normal subjects react differently (Hurtado and others⁴⁴) We are also unable to explain why some patients react to the anoxemia produced by the hypoventilation with an increase in the red cell volume and why others do not This difference has also been pointed out by Kaltreider, Hurtado and Brooks⁴³

Since the higher values were obtained in patients with heart failure, the possibility exists that this condition may be the cause of a further increase in blood volume Nevertheless, as these patients were also those in whom the lower values for oxygen saturation were found, we are unable to decide whether heart failure is a contributing factor or not

Determination of blood volume in Ayerza's disease has been made previously in only 1 case by Lemon,⁶⁵ who also observed a decided

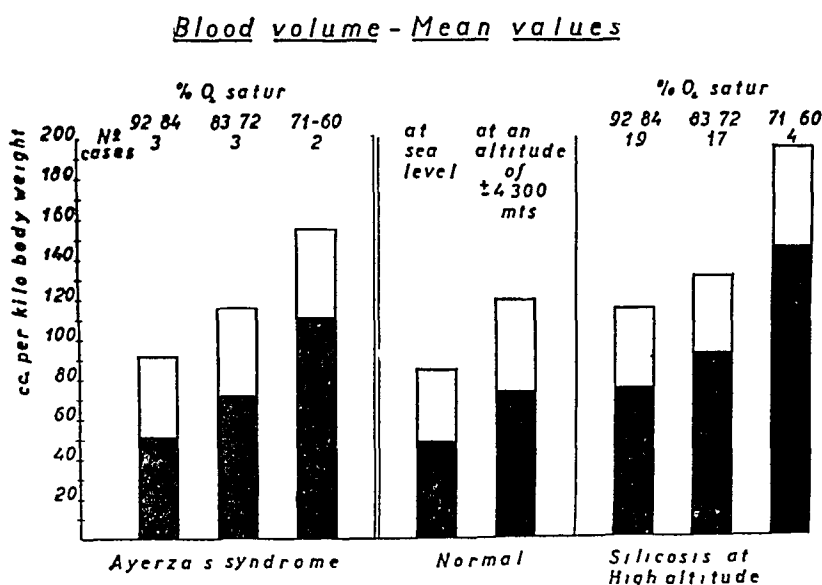


Fig 2—Data obtained on the mean values for the blood volume in the group with Ayerza's syndrome were compared with those obtained by Hurtado, Merino and Delgado⁴⁴ in normal persons at sea level and at high altitude and in persons with silicosis at high altitudes

increase in the red cell volume The changes in blood volume observed in these patients parallel those found by several workers in other types of anoxemia Our results agree with those obtained in normal subjects at high altitude by Lippmann,⁶⁶ Lozoya Solis⁶⁷ and Hurtado and others⁴⁴ They also agree with the results obtained by Hurtado⁶⁸ in

65 Lemon, W S A Study of the Effect of Chronic Pulmonary Diseases on the Volume and Composition of the Blood, *Ann Int Med* 3 430, 1929

66 Lippmann, A Blutzusammensetzung und Gesamtblutmenge bei Hochgebirgsbewohnern, *Klin Wchnschr* 5 1406, 1926, cited by Hurtado and others⁴⁴

67 Lozoya Solis, J El volumen de plasma y de sangre circulantes en las altitudes y sus variaciones con la tiempo y con el ejercicio muscular, *Arch latino am cardiol y hemat* 6 241, 1936, cited by Hurtado and others⁴⁴

patients with Monge's disease and by Hurtado and his colleagues⁴⁴ in patients with silicosis at high altitude

Cardiac Output (Table 15)—The well known difficulties in applying the rebreathing methods in subjects with gross alterations in the lungs, present in our patients, raise the question of whether the results are reliable or not

Among all the cases, we chose for studying this function those in which the vital capacity and respiratory mechanisms seemed capable of allowing for the rebreathing technic

The data in table 16 indicate the possibility of attaining a homogeneous mixture in the lung bag system before noticeable recirculation occurs. It shows the values of the arteriovenous oxygen difference

TABLE 15—*Cardiac Output and Related Functions*

Case	Age	Body Surface,* Sq M	Heart Rate, per Min	Oxygen Consumption, Cc /Min	Arteriovenous Oxygen Difference, Cc /L	Cardiac Output, L /Min	Cardiac Index, L /Sq M	Systolic Output, Cc	Systolic Output, Cc / Sq M
2	46	1.72	84	232	52.3	4.44	2.58	53	30.7
			87	223	50.5	4.41	2.56	51	29.5
3	53	1.99	67	254	69.0	3.68	1.85	55	27.6
			65	248	75.0	3.31	1.66	51	25.6
6	55	1.78	64	235	56.2	4.18	2.35	65	36.7
			60	233	61.9	3.76	2.11	63	35.4
			61	231	62.4	3.70	2.08	61	34.1
10	64	1.69	87	231	102.7	2.25	1.33	26	15.3
			87	225	109.9	2.05	1.21	23	13.9
			83		111.2	2.02	1.20	24	14.2
11	47	1.93	87	308	76.0	4.05	2.10	46	24.1
			94	303	64.0	4.73	2.45	50	26.1
12	65	1.85	64	217	74.2	2.92	1.58	45	24.7
			64	221	74.6	2.96	1.60	46	25.0
16	54	2.04	79	307	71.1	4.31	2.12	55	26.7
			78	311	70.9	4.39	2.15	56	27.6

* Edema free weight

calculated between each pair of successive samples of the best determination on each subject. As can be seen, in every case it was possible to get at least two consecutive values for arteriovenous oxygen difference agreeing within highly satisfactory limits, the worst deviation being — 5.4 per cent from the mean in case 2.

Another test for the possibility of a good mixture in the lung bag system during rebreathing was elaborated, advantage being taken of the serial alveolar air experiments (table 17).

The subject in case 7 (R A) was chosen for this purpose because in the usual conditions there had been great differences in his successive samples of serial alveolar air. He was instructed to take a deep inspiration and then to expire gradually in a six second period as thoroughly

as he could. During this time four instantaneous samples were taken when the subject had expired 500, 1,000, 1,500 and 2,000 cc respectively (the last at the end of the six seconds). Several minutes later and after a deep expiration he had to rebreath from a bag containing 2,400 cc of air, which simulated an ordinary cardiac output experiment. After twenty-two seconds of rebreathing, the three way cock was turned instantaneously at the end of a deep inspiration. The following deep expiration lasted six seconds and during it serial alveolar air samples were taken, as stated before. During these tests, moderate bronchial spasm was present.

TABLE 16—*Detailed Results of Arteriovenous Oxygen Difference in the Most Reliable Test on Each Subject*

Case		2	3	6	10	11	12	16
Arteriovenous oxygen difference calculated between	{ Samples 1 and 2	81.0	66.2*	61.3	111.2	82.6	74.6	57.0
	{ Samples 2 and 3	55.2	69.0	64.6	108.6	76.0	73.8	68.8
	{ Samples 3 and 4	49.5	71.9	59.8	123.5	76.0	117.6	73.5
Accepted arteriovenous oxygen difference		52.3	69.0	61.9	109.9	76.0	74.2	71.1

* The figures in bold face were those considered valuable for the calculation of the accepted value.

TABLE 17—*Serial Alveolar Air Before and Immediately After 22 Seconds of Rebreathing in Case 7*

	Samples	I	II	III	IV
Before rebreathing	{ Volume of expired air in cc	500	1,000	1,500	2,000
	{ CO ₂ , per cent	7.50	8.13	8.78	9.42
	{ O ₂ , per cent	13.04	11.75	10.00	8.23
Immediately after rebreathing	{ Volume of expired air in cc	500	1,000	1,500	1,750
	{ CO ₂ , per cent	10.06	10.14	10.20	10.21
	{ O ₂ , per cent	9.16	8.74	8.21	7.88

The results in table 17 show that the maximal difference in carbon dioxide concentration in the four samples changed from 1.92 per cent in the first test to 0.15 per cent after the rebreathing. The behavior of the oxygen was satisfactory, the difference being 4.81 per cent before and 1.28 per cent after the rebreathing.

The mixture obtained in this case from deep rebreathing after a short period of rebreathing suggests that at least in some of the patients a homogeneous mixture could be obtained at the moment of the sampling in determinations of cardiac output. This in turn is in accordance with our data on arteriovenous oxygen difference discussed previously, and the two together give a strong support to the validity of the findings on cardiac output in our series.

In order to avoid changes in arterial saturation during the rebreathing period in cases in which there was low tension of alveolar oxygen,

mixtures were prepared to keep the average oxygen tension in the rebreathing samples as near as possible to that of the alveolar air. The difference between the two values for cardiac output in the subject in case 11 (table 15) may be ascribed to the fact that oxygen tension in the rebreathing samples was higher the first time and lower the second time than that of the alveolar air. The average may be considered as a better approximation to the true value for cardiac output.

Finally, even though the existence of a perfect equilibrium between alveoli and blood after the use of acetylene was not proved in our cases, we may accept it since Grollman and others,⁶⁹ using the acetylene method in patients with heart failure, pulmonary alterations and slight degree of arterial unsaturation, found alveolar-blood equilibrium in every case in which a homogeneous mixture in the lungs could be obtained.

In summary, it seems to us that determinations of cardiac output in our patients are reliable, but a direct unquestionable demonstration is lacking.

The subjects in cases 2, 16 and 6, who had never had cardiac insufficiency or signs of cardiac involvement, had a normal cardiac index (2.5, 2.1 and 2.2 respectively). The arteriovenous oxygen difference was normal in the first and third cases and higher than our normal limits in the second case (Suarez, Fasciolo and Taquini⁷⁰).

The subject in case 11, who was under digitalis therapy because he had had cardiac failure, had a normal cardiac index. The patient in case 3, also with a history of heart failure, showed a diminished cardiac index.

The subjects in cases 12 and 10 were obviously in congestive failure. The former had a diminished cardiac index (1.6), with an arteriovenous oxygen difference in the highest normal range. The other had an extremely low cardiac index (1.2), with an increased arteriovenous oxygen difference.

The systolic output per square meter of body surface was diminished in all cases but 1 (case 6).

Our results indicate that in cases in which only respiratory insufficiency was present cardiac output was maintained at normal levels irrespective of the type of pulmonary alterations and the degree of arterial oxygen unsaturation and polycythemia. When cardiac insufficiency was added, cardiac output was diminished. This suggests a

69 Grollman, A., Friedman, B., Clark, G., and Harrison, T. R. Studies in Congestive Heart Failure. XXIV. A Critical Study of Methods for Determining the Cardiac Output in Patients with Cardiac Disease, *J. Clin. Investigation* **12** 751, 1933.

70 Suarez, J. R. E., Fasciolo, J. C., and Taquini, A. C. Cardiac Output in Heart Failure, *Am. Heart J.* **32** 339, 1946.

direct correlation between functional capacity of the heart and cardiac output levels similar to that found in most of the cases of common heart disease (Suarez, Fasciolo and Taquini ⁷⁰)

Almost all the available data in the literature about patients with Ayerza's syndrome were secured with the indirect Fick method similar to that of Field, Bock and others ⁷¹ In this way, Ayerza, Solari and Berconsky ¹⁴ and Arrillage, Berconsky and Taquini ¹⁵ obtained normal values On the contrary, Cossio and Berconsky ⁷² and Capdehourat ¹⁸ found diminished cardiac outputs These different results seem likely to be explained on the basis of the distinct cardiac involvement, as suggested by their protocols

TABLE 18—Average Values of p_H and Oxygen and Carbon Dioxide Pressures of the Arterial and Venous Blood of Patients Suffering from Ayerza's Syndrome

	Arterial Blood*			Mixed Venous Blood		
	Pulmonary Anoxemia with Increased Hemoglobin			Pulmonary Anoxemia with Increased Hemoglobin		
	Normal Persons	Not in Heart Failure	In Heart Failure	Normal Persons	Not in Heart Failure	In Heart Failure
pO_2 , mm Hg	95.00	48.7	47.7	35.00	31.7	28.0
pCO_2 , mm Hg	41.00	55.4	53.0	49.00	60.5	62.0
p_H	7.40	7.34	7.33	7.36	7.32	7.31

* Arterial values were obtained by direct analysis Venous values were calculated from the arterial values and the arteriovenous difference

A special consideration of Richards' data ⁷³ is necessary This author studied 6 cases of "cor pulmonale" with the method of catheterization of the right side of the heart and found normal cardiac outputs and arteriovenous oxygen differences The paper gives only summarized data and does not allow for further consideration of the criteria used by the author for judging cardiac insufficiency

COMMENT

Previous results showed that emphysematous patients have a decreased amount of tidal air and an uneven distribution of gases in the lungs As a consequence, the efficiency of ventilation is decreased

71 Field, H , Bock, A V , Gildea, E F , and Lathrop, F L The Rate of the Circulation of the Blood in Normal Resting Individuals, J Clin Investigation 1 65, 1924

72 Cossio, P, and Berconsky, I Sindrome de hipoventilacion alveolar Estudio clinico y fisiopatológico de tres "cardiacos negros" (con una necropsia) Semana med 2 917, 1932

73 Richards, D W, Jr Cardiac Output by the Catheterization Technique, in Various Clinical Conditions, Federation Proc 4 215, 1945

In the early stage of the disease, full or partial compensation is achieved by increasing the respiratory minute volume, mostly as a result of auxiliary mechanisms of respiration. In the more advanced stages, when the diaphragm is lowered and the thorax is rigid, the ventilation of the lungs is not increased or decreased. As a consequence, the ventilation of the alveoli is impaired and carbon dioxide increases and oxygen decreases.

The low alveolar oxygen tension produces different degrees of anoxemia which stimulate the bone marrow and produce the hyperglobulia and the increase in hemoglobin present in the great majority of our patients. These changes keep the oxygen content of arterial blood around normal or slightly higher. On the other hand, the increase in the carbon dioxide tension leads to an increase in the BHCO_3 of plasma. Nevertheless, full compensation is not reached since p_{H} is slightly lower in these patients than in normal persons.

The changes in blood previously mentioned are important since they allow the patients to endure carbon dioxide and oxygen tensions that could not be endured by normal subjects.

Since these patients are able to increase their ventilation, either willingly or by breathing carbon dioxide, the question arises of why they have normal or only slightly increased ventilation, notwithstanding the low oxygen pressure, high carbon dioxide pressure and low p_{H} of their arterial blood. These paradoxical findings have been explained by the postulation of a depression of the respiratory center due to chronic anoxemia. However, chronic anoxemia does not seem to have a depressor effect on respiration since patients with cyanotic congenital heart diseases have increased pulmonary ventilation. It is possible to explain these findings without postulating a depression of the respiratory center by admitting that the abnormalities of the chest and lungs reduce ventilation although the nervous discharge of the neurons at the respiratory center is adequate for the composition of the blood at that moment.

Circulatory Changes—Previous results show that in patients with Ayerza's syndrome without heart failure the cardiac output and the arteriovenous difference are normal. On account of the high viscosity of the blood the arterial pressure should increase, producing an overload of the anoxic cardiac muscle, for the maintenance of a normal cardiac output. Such a condition is avoided by increasing the blood volume and the vascular bed. These adaptations make the maintenance of normal cardiac output and a normal arteriovenous difference possible without a serious increase in peripheral resistance and with an extremely slow blood velocity, that is to say, without an increase in the cardiac work. In fact, the time employed by the blood to complete the circuit was calculated by dividing the blood volume by the cardiac output and

the average value found was nearly double the normal value as calculated in the same way. The slow blood velocity and the normal arteriovenous difference indicate that the blood flow per unit of time is normal. Such a result can be produced only by an increase of the capillary bed and of the total blood volume. It is interesting to note that although a normal oxygen content of arterial blood (volumes per cent) could have been obtained by merely decreasing the plasma volume, i.e., concentrating the cells to maintain a normal arteriovenous difference, blood velocity should increase.

The previously discussed mechanism nearly compensates the arterial changes produced by hypoventilation. As a result venous blood, which in turn can be accepted as a measure of the environmental condition of tissues, approaches normal, as table 18 shows. These results show that under basal conditions the tissues are maintained not far from normal. Moreover, since there is a great increase of the vascular bed and probably an opening of new capillaries, it is possible that distances from capillary to capillary are diminished. Then oxygen and carbon dioxide gradients should be smaller, and the conditions of cells could be further improved.

SUMMARY

In the group of pulmonary patients with mild to severe anoxemia pulmonary ventilation was found slightly increased, alveolar carbon dioxide tension was found to be higher and oxygen tension lower than in normal persons, indicating that alveolar ventilation was impaired. This alveolar hypoventilation in cases in which pulmonary ventilation was normal or even increased is produced by poor efficiency of ventilation. In our series the low efficiency was due to (a) uneven distribution of gases in the lung and (b) diminution of tidal air.

The main pulmonary disturbance of the group with Ayerza's disease was emphysema of the lung, as reflected by the figures of the total pulmonary capacity and its subdivisions. Vital capacity was found to be diminished, mainly because of a reduction of complemental air, reserve air being about normal. Residual air was increased, and total pulmonary capacity was slightly reduced. In some patients the basal metabolic rate was over the normal figures.

The oxygen dissociation curve of arterial blood at p_H 7.40 and 37 C was not appreciably different from that of normal persons. At arterial p_H , owing to slight acidity of the blood, the curve was displaced to the right.

The oxygen capacity of blood was increased, keeping an inverse coarse correlation with the arterial oxygen pressure. The increase in hematocrit values was greater than that of hemoglobin, that is to say, the hemoglobin content per hundred cubic centimeters of cells was less than that in normal persons at sea level or at high altitude. The water content of red cells was increased in the 3 cases in which it was determined.

Arterial oxygen saturation and pressure were reduced below normal values in all the cases. The oxygen content of arterial blood of the group with Ayeiza's disease was slightly elevated when compared with that in normal persons at sea level.

The alkaline reserve of plasma was increased, but that of the whole blood was normal on account of increased red cell volume. Values for carbon dioxide pressure and total carbon dioxide content of arterial blood were higher and for p_H lower than those in normal persons, which indicates a primary excess of carbon dioxide.

The alveolar-arterial oxygen difference was increased, and the evidence presented indicated that such an increase can be satisfactorily explained on the basis of unequal distribution of gases in the lung. Carbon dioxide pressure between alveoli and blood was not clearly increased.

That the arterial anoxemia was stimulating the breathing in these patients, probably through the carotid and aortic bodies, was shown by the depression of ventilation produced while they were breathing pure oxygen.

Breathing pure oxygen during seventeen to thirty minutes increased the arterial carbon dioxide pressure and decreased the p_H . The arterial oxygen rose to a pressure of about 300 mm of mercury, less than that in normal persons under the same conditions. This finding is consistent with the hypothesis that the anoxemia is the result of an uneven ventilation of the alveoli.

The response to inhalation of carbon dioxide was less than that of normal persons. It was pointed out that this finding does not necessarily mean depression of the respiratory center.

In 8 of 12 cases the response to inhalation of carbon dioxide was greater when air was breathed than when oxygen was breathed, which suggests that in these cases the anoxemia had potentiated the respiratory center answer to carbon dioxide.

Venous pressure was higher than 150 mm of water only in 4 cases of cardiac failure.

Ether and "dechlorin" circulation times were prolonged in almost every case.

The blood volume was increased, which was due primarily to an increase in red cell volume. The increase was roughly related to the degree of anoxemia. Changes in plasma volume were of minor importance.

Cardiac output was maintained at normal levels in cases uncomplicated by cardiac failure. When cardiac insufficiency was superimposed, diminished values were obtained.

The calculated oxygen pressures at the tissue levels in patients without cardiac failure was close to normal.

ACQUIRED ACUTE HEMOLYTIC ANEMIA OF UNKNOWN CAUSE

*Report of a Case with Fibrinoid Arteritis, Atypical
Pneumonia and Lower Nephron Nephrosis*

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THE RATHER scanty data on the lesions of acute hemolytic anemia have been reviewed recently by Damashek and Schwartz¹ and may be summarized briefly. Of 29 cases in which histologic changes in the spleen were described, hyperplasia of reticular or histiocytic cells with giant cell formation, erythrophagocytosis and myeloid metaplasia was prominent in 12, multiple infarction with thrombosis of veins and capillaries, in 6, and extreme hyperemia of the pulp, said to be similar to that in congenital hemolytic icterus, in 11. The spleens were enlarged from one and one-half to six times. Bone marrow was described as showing normoblastic hyperplasia in a few cases. Of the 10 necropsies in which the liver was examined hemosiderosis was noted in all but 1, which showed acute yellow atrophy. "Hemoglobinous infarcts" were described in a case in which a lethal reaction to transfusion had occurred.

The present case is reported partly because of the paucity of published data, but chiefly because of the fibrinoid vascular lesions, the lower nephron nephrosis and the unusual type of pneumonia.

REPORT OF CASE

History and Physical Examination—The patient, a 20 year old white woman, of Italian descent, had been well all her life except for intermittent attacks of thrombophlebitis in the left leg. One month before her admission to Stanford Hospital she had had several "injections" for varicosities of the left leg. After the injections she lost her appetite and noticed increasing swelling of the left leg. Two weeks before her admission icteric scleras were observed, and she began to have attacks of nausea and vomiting with severe headaches and with pain in the chest. Three days before entry jaundice of the skin developed. She was hospitalized elsewhere for a condition diagnosed as acute leukemia and received four transfusions and penicillin. After two days, during which dyspnea, high fever and edema of the face developed, she was transferred to Stanford Hospital, on Dec 21, 1947. On admission she was described as acutely ill,

From the Department of Pathology, Stanford University School of Medicine.

1 Damashek, W, and Schwarz, S O. Acute Hemolytic Anemia (Acquired Hemolytic Icterus, Acute Type), *Medicine* 19 231 (May) 1940.

semicomatose and extremely dyspneic Her face and left leg were edematous and her skin was jaundiced There were signs of consolidation in the lower lobe of the right lung, the abdomen was distended, and liver and spleen appeared enlarged on percussion There was generalized enlargement of the lymph nodes

TABLE 1—*Clinical Data in a Case of Acquired Acute Hemolytic Anemia*

Date	Urinary Volume, Cc/24 Hr	Specific Gravity of Urine	Blood Urea, Mg/100 Cc	Blood Pressure	Erythro- cytes, Mil lions	Hemo- globin, Gm/100 Cc	Transfusions, Cc		Fluid Intake, Cc	
							Whole Blood	Red Cell Con- centrate	Oral	Paren- teral
12/21	875	1 011	60		2 43	8 5	250	500	1,150	
12/22	1,820				2 56	10 3	500		2,570	
12/23	2,600		60		1 77	7 04			2,360	
12/24	1,880				0 97	4 52		1,000	2,500	
12/25	2,160				1 66	4 87			2,510	
12/26	880+	1 012			0 95	3 13	500		920	
12/27	400+	1 011			2 35	7 13		1,000	200	3,000
12/28	540+			130/70				1,000	360	2,000
12/29	1,070			146/90				1,000	845	2,000
12/30	670+				3 7	13 39			520	2,000
12/31	1,520+	1 009	288	150/90	3 7	13 48			1,530	800
1/1	1,740			150/80					1,640	
1/2	1,010+	1 008	324		2 8	8 87			630	2,000
1/3	2,250	1 010	318		1 73	6 69		1,000	150	3,000
1/4	2,600			118/70	2 27	7 13		500	100	3,000
1/5	2,350				2 2	8 78		500	15	2,000
1/6	3,000		228						620	3,000
1/7			285		2 3	8 0	500			

TABLE 2—*Leukocyte Count in Case of Acute Hemolytic Anemia*

Date	Differential White Cell Count, per Cent								
	Total White Cells	Neutrophils		Eosino phils	Baso phils	Lympho cytes	Mono cytes	Myelo cytes	Nucleated* Red Cells
		Banded	Seg- mented						
12/21	18,600	16	54	0	1	26	3	0	36
12/23	10,800	49	17	1	1	25	1	7	16
12/26	32,600	14	45	1	1	29	5	5	38
12/30	10,878	45	35	1	0	18	0	0	2
1/4	48,100	52	26	2	1	14	4	0	2
1/6	31,100	48	35	0	0	12	1	6	9
1/7	45,700	66	16	0	0	14	0	4	25

* Count per hundred leukocytes

Laboratory Findings (tables 1 and 2)—Fragility of erythrocytes, tested on December 23, was within normal limits Prothrombin time on December 27 was 49 per cent of normal The platelet count was 160,000 per cubic millimeter on December 21 and 100,000 on December 27 On December 31 the mean corpuscular volume of the erythrocytes was 129 cubic microns, the mean corpuscular hemoglobin was 36 micromicrograms and the mean corpuscular hemoglobin concentration was 28 per cent On several occasions the urine was cherry red, but no hemoglobin determinations were carried out on it On December 21 there were about 5 granular casts and a rare erythrocyte per high power field in the centrifuged specimen On December 31 and on January 2 and 6 no casts were observed in the urine There were a few erythrocytes No quantitative studies were carried out on formed elements in the urine The patient's blood

was type O and she was Rh negative. Difficulty was experienced in obtaining compatible blood for transfusion, as the patient's serum contained atypical agglutinins with a wide range of action.

Course of Illness—The patient was treated with multiple transfusions of red cell concentrate, plasma and whole blood (table 1). During the first four days her temperature remained about 39 C (102.2 F), but dropped on the fifth day, and her condition seemed improved. There was roentgenographic evidence at this time of some clearing of the pneumonia in the lower lobe of the right lung. Although her temperature remained lower for the next week, the improvement was only temporary. She became confused and disoriented. On the ninth day edema of the legs was noticed, and on the eleventh day the blood urea was 288 mg per hundred cubic centimeters. Her temperature rose again on the



Fig 1—Spleen, $\times 150$, hematoxylin and eosin stain. Infiltration and destruction of wall of trabecular vein.

thirteenth day, and she died rather suddenly on the eighteenth day after admission. The clinical diagnoses were acute hemolytic anemia, pneumonia of the lower lobe of the right lung, acute nephritis and thrombophlebitis of the left iliac vein.

Autopsy (seven hours after death)—The skin and mucous membranes were intensely icteric. There was generalized subcutaneous edema. The diameter of the left leg was about one and one-half times that of the right. There were approximately 800 cc of clear, yellowish green fluid in the left pleural cavity, 1,500 cc in the right pleural cavity and 300 cc in the peritoneal cavity. All the viscera were yellowish brown. The heart weighed 360 Gm and was not remarkable except for an area of hyperemia, 2 cm in greatest dimension, in the interventricular septum. The foramen ovale was closed. The left lung weighed 520 Gm, the cut surface was edematous, and there were areas of con-

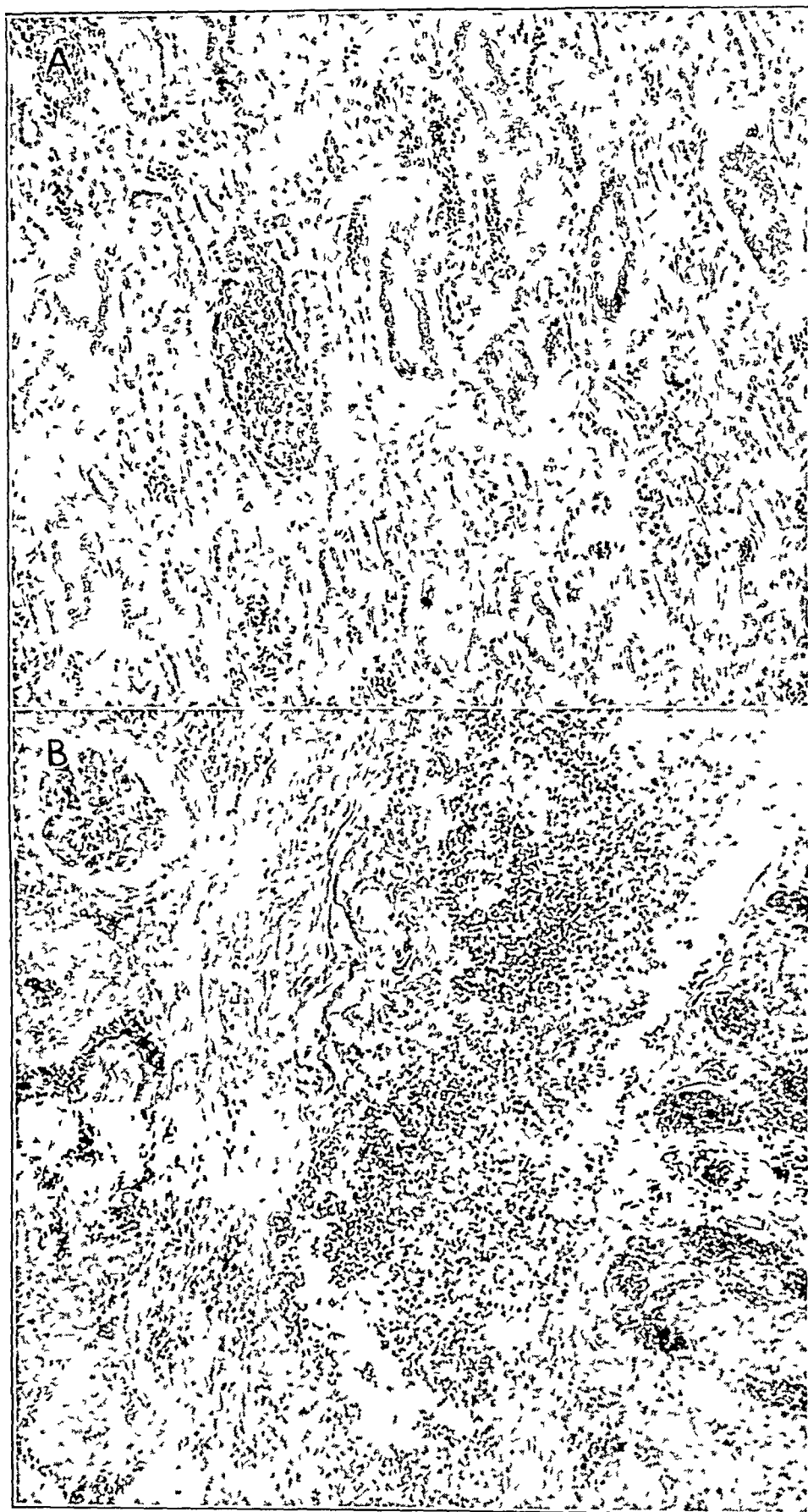


Fig 2—Kidney, $\times 150$, hematoxylin and eosin stain *A*, pigmented casts in collecting tubules, cellular infiltrate *B*, rupture of necrotic tubule into vein parietal thrombosis

gestion but no consolidation. The right lung weighed 790 Gm, and on the external surface there were many intense purple blotches, which, on section, were observed to be granular and appeared to be small infarcts, although dissection of the pulmonary arteries revealed no thrombi. There was irregular consolidation of the lower lobe of the right lung. The liver weighed 2,700 Gm and was bile stained. The lobular markings were visible. The spleen weighed 900 Gm, and, on section, there were noted many firm, yellowish gray areas of infarction, averaging 4 cm in greatest dimension. The kidneys weighed 260 and 270 Gm. When dissected, they appeared somewhat bile stained but were otherwise not remarkable. The pelvic veins on the right were normal. The left iliac vein was completely thrombosed at a point 7 cm from the bifurcation of the vena cava, with some extension up toward the vena cava.

Microscopic Examination—Liver. The areas about the central veins of the liver were hyperemic, and the sinusoids everywhere were crowded with erythrocytes. Phagocytosis of erythrocytes by the Kupffer cells was definite and widespread. Many of the Kupffer cells contained masses of pigment, varying from light green to brown, most of the latter reacting to form prussian blue. The majority of the hepatic cord cells contained similar masses of pigment, some of which reacted to form prussian blue.

Spleen. The red pulp was packed with erythrocytes, reticular cells and plasma cells. There were many giant forms of reticular cells with huge, basketwork-like nuclei. These contained fragments of red cells. A large amount of intracellular pigment was present, much of which reacted to form prussian blue. The malpighian follicles were small, and the germinal centers were not active. There were fibrinoid alteration of the wall of a trabecular vein and infiltration of the wall by mononuclear cells (fig 1). A few of the trabecular veins contained thrombus material. There were areas of recent infarction. Scattered throughout the pulp were collections of large cells with basophilic cytoplasm and large nuclei. Some of the cells had mitotic figures and suggested myeloid metaplasia.

Kidneys. In the cells of the proximal convoluted tubules, there were numerous small, brown granules which reacted to form prussian blue. These tubules were large and had the appearance of the hypertrophied nephrons observed in certain cases of chronic glomerulonephritis. In the boundary zone and pyramids were lesions characteristic of lower nephron nephrosis,² i. e., interstitial cellular infiltration, damaged collecting and distal tubules, pigmented casts within these tubules, (fig 2A) and rupture of necrotic tubules into thin-walled veins (fig 2B). In addition, there was evidence of myeloid metaplasia in the pyramids. This change took the form of clumps of basophilic cells, some in mitosis, lying within and adjacent to dilated capillaries in the medulla.

Vertebral Marrow. There was hyperplasia of all elements, particularly of the erythrocytic series. The erythrocytic hyperplasia was of the normoblastic type. No hemosiderin or other pigment was present.

Vascular Lesions. Those in the pancreas were best developed and will be described in detail. Figure 3A shows a pancreatic artery, with a diameter of about 300 microns. In the hematoxylin and eosin preparation, the collagen of the adventitia had a swollen, glassy, refractile appearance and was brightly eosinophilic. The muscular layer was interrupted at several points by a similar fibrinoid alteration. Surrounding the small artery was a scanty infiltration con-

2 Lucké, B. Lower Nephron Nephrosis, *Mil Surgeon* 99 371 (Nov) 1946

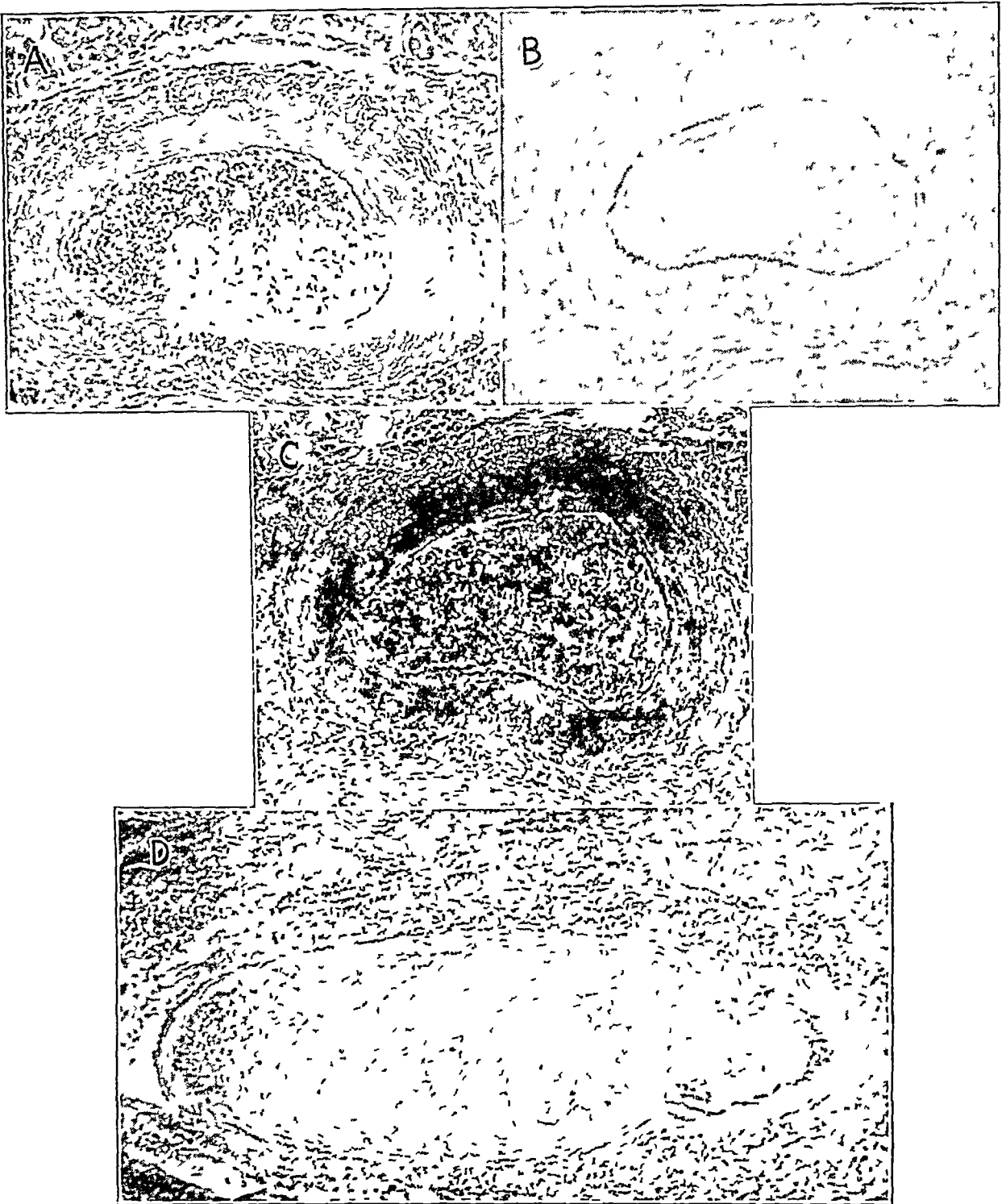


Fig 3—*A*, pancreatic artery, 300 microns diameter, $\times 150$, hematoxylin and eosin stain. Thickened refractile collagen in adventitia. *B*, same artery, Van Gieson-Weigert stain, showing breaks in internal elastic membrane. *C*, same artery, azocarmine stain. The red-stained fibrinoid appears black. Involvement of entire thickness of the wall is shown. *D*, splenic artery, Van Gieson-Weigert stain, $\times 150$. Destruction of internal elastic membrane and muscular wall.

sisting chiefly of large mononuclear cells with a few polymorphonuclear leukocytes and rare eosinophils. In the Van Gieson-Weigert preparation, the altered collagen and muscle stained yellow, whereas nearby normal collagen stained red, and at the

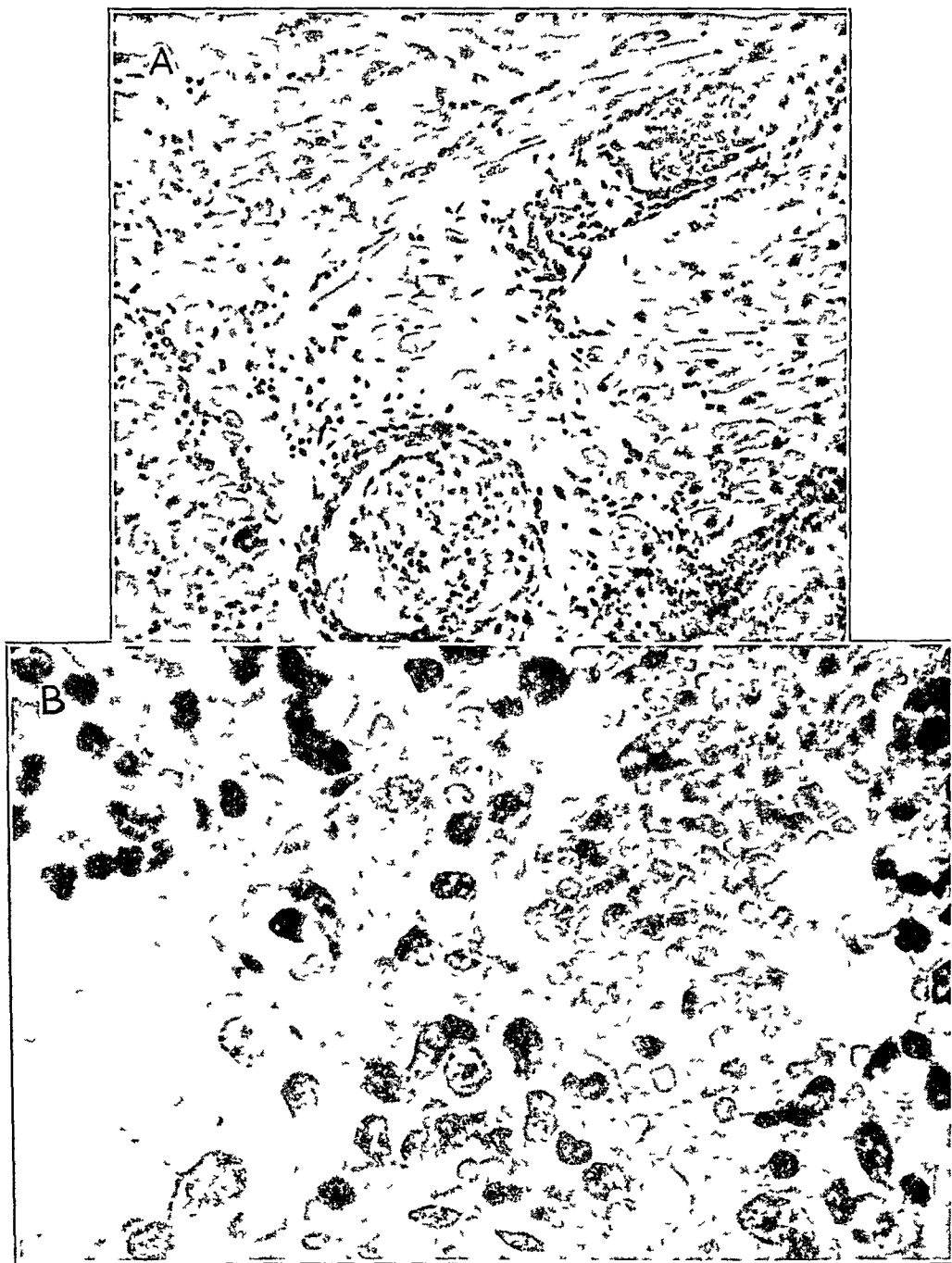


Fig 4—*A*, heart, $\times 150$, hematoxylin and eosin stain. Thrombosis of small veins. *B*, right lung, $\times 450$, hematoxylin and eosin stain. Atypical pneumonia in lower lobe.

points where the wall of the vessel was most involved the yellow material extended through to replace the internal elastic membrane, interrupting its continuity at

several points, as shown in figure 3*B*. In the azocarmine preparation (Heidenhain modification), the altered collagen and muscle of the vascular wall stained a brilliant red, appearing black in figure 3*C*, and the involvement of the entire thickness of the arterial wall at several points was clearly shown. In the phosphotungstic acid-hematoxylin stain, the fibrinoid substance appeared a deep purplish black, while normal collagen stained yellowish orange. Most of the arteries of comparable caliber in this section of the pancreas were involved. There was no thrombosis. An artery in the spleen, with a diameter of about 350 microns and lying in the center of an infarcted area, showed destructive thrombosing arteritis. In the Van Gieson-Weigert preparation (fig 3*D*) the localized destruction of the muscular wall and internal elastic membrane was well shown. The infarct in the interventricular septum was estimated to be about twenty-four hours old. In the involved area there were many arterioles, with diameters of about 100 microns, which showed alterations in the internal elastic membrane and muscularis. Most of these vessels were thrombosed. There were thrombi in several small venules of the myocardium (fig 4*A*). Similar thrombi were present in venules of the parathyroid glands.

Lungs. No vascular lesions of the sort observed in the pancreas were seen in the lungs, although there were organizing thrombi in some of the smaller vessels. One large vessel contained an unattached embolus, which appeared to have broken off from an organizing thrombus in the left iliac vein. Nearby was a small early infarct. Involving most of the lower lobe of the right lung was a pneumonia characterized by the presence of a peculiar interstitial infiltrate (fig 4*B*). The infiltrating cells were plasma cells, lymphocytes and large mononuclear leukocytes. Some cells of the last type had very large nuclei and basophilic cytoplasm with tapered ends. Infiltration with polymorphonuclear leukocytes was relatively slight, and the bronchi were not primarily affected. Many of the alveoli contained fibrin, and there were fibrin plugs in the alveolar capillaries. There was widespread intra-alveolar hemorrhage. Megakaryocytes were numerous in the alveolar capillaries. No organisms were demonstrable in the bacterial stains. The anatomic diagnoses were hemosiderotic pigmentation of the liver, spleen and kidney, ascites, hydrothorax and subcutaneous edema, edema of the lungs, chronic passive hyperemia of the liver and spleen, normoblastic hyperplasia of the bone marrow, thrombosis of the left external iliac vein with pulmonary embolism and multiple small infarctions, atypical pneumonia of the lower lobe of the right lung, lower nephron nephrosis, disseminated fibrinoid arteritis involving the pancreas, spleen and myocardium, recent infarction of the myocardium (interventricular septum) and spleen, and myeloid metaplasia of the spleen.

COMMENT

The cause of the acquired acute hemolytic anemia in this case was not determined. There was no morphologic abnormality of the erythrocytes, nor was their fragility increased. It is clear from the data in table 1, however, that transfused red cells were destroyed as fast as they were given. Very little hemoglobin was excreted in the urine, as far as can be judged from the available data. The data in table 1 also suggest that the volume of the urine was insufficient in relation to its low specific gravity. The persistent increase in blood urea was probably a consequence of the large amount of protein given intra-

venously despite renal insufficiency attributable to lower nephron nephrosis Lucké² stated the belief that lower nephron nephrosis follows the destruction of large amounts of tissue or of blood, the latter condition was amply fulfilled in this case. It has been demonstrated that parenterally injected protein will maintain nitrogen balance in dogs,³ and Addis⁴ showed that in rats parenterally injected protein leads to great increase in urea in the urine. He pointed out that 1 liter of blood contains about 167 Gm of protein (plasma protein plus hemoglobin), and stressed the potential danger in giving large amounts of blood in the presence of renal insufficiency.

Venous thrombosis has been described in cases of acute hemolytic anemia,¹ and in the case described here such thrombi were noted in small veins of the heart, parathyroid glands and spleen. The arterial lesions, however, were apparently unique. They were indistinguishable from those seen in cases of lupus disseminatus and periarteritis nodosa and were of the type stated by Rich and Gregory⁵ to be indicative of hypersensitive reactions and by others⁶ to be indicative of sharply rising hypertension. Table 1 shows only a mild, transient elevation of blood pressure in this case. The nature of the injections given one month prior to the patient's admission was not determined. In view of the time interval and the early development of the vascular lesions, the injections are unlikely to have been implicated in the pathogenesis. Sulfonamide compounds were not given at any time during the patient's stay at Stanford Hospital.

The atypical pneumonia closely resembled the type described by Rich⁷ as characteristic of pneumonitis seen in rheumatic fever and in sensitization to sulfonamide drugs, and which he asserted to be of anaphylactic origin. No bacteriologic studies were carried out clinically. Morphologically, the process was not of the type seen in bronchopneumonia or lobar pneumonia, nor were organisms demonstrable in bacterial stains of the tissue. It is possible that the hemolysis,

3 Madden, S. C., and Whipple, G. H. Plasma Proteins. Their Source, Production and Utilization, *Physiol Rev* **20** 194 (April) 1940.

4 Addis, T., Barrett, E., Lew, W., Poo, L. J., and Yuen, D. W. Danger of Intravenous Injection of Protein Solutions After Sudden Loss of Renal Tissue. *Arch Int Med* **77** 254 (March) 1946.

5 Rich, A. R., and Gregory, J. E. Experimental Demonstration That Periarteritis Nodosa Is Manifestation of Hypersensitivity, *Bull Johns Hopkins Hosp* **72** 65 (Feb.) 1943.

6 Smith, C. C., Zeek, P. M., and McGuire, J. Periarteritis Nodosa in Experimental Hypertensive Rats and Dogs, *Am J Path* **20** 721 (July) 1944.

7 Rich, A. R., and Gregory, J. E. On Anaphylactic Nature of Rheumatic Pneumonitis, *Bull Johns Hopkins Hosp* **73** 465 (Dec.) 1943.

the vascular lesions and the pneumonitis were all expressions of damage caused by a circulating antigen to which the patient was sensitized

SUMMARY

A case of acquired acute hemolytic anemia of unknown cause is presented. The lesions, in particular disseminated fibrinoid arteritis, an atypical pneumonia and lower nephron nephrosis, are described and discussed.

Stanford University School of Medicine

LUTEMBACHER'S SYNDROME

Report of a Case with Unusually Large Atrial Septal Defect

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IT IS somewhat paradoxical that often, even in persons of advanced years, the question of possible congenital cardiac disease enters prominently into the problems of differential diagnosis and prognosis. The commonest of all congenital defects, patent foramen ovale, frequently gives rise to no symptoms or signs throughout life and is discovered only at autopsy. Lutembacher's syndrome, a large atrial septal defect with concomitant mitral stenosis,¹ is an extremely uncommon combination of congenital lesions, which often does not become apparent until late in life, and the diagnosis of which is likely to be missed until autopsy. McGinn and White,² however, in 1933, pointed out that this combination of lesions may well be recognized before death if the possibilities of its occurrence and the distinctive roentgenographic findings are borne in mind, and Geiger and Anderson³ have recently recorded a case in which the diagnosis was made ante mortem.

In the case of Lutembacher's syndrome recorded in this communication the atrial defect is believed to be the largest reported to date.

REPORT OF CASE

History—G E R, a white man aged 31, was first seen on July 22, 1942, when the following history was obtained:

He had been considered a delicate, highly nervous child, though nothing in any way abnormal could be elicited concerning the neonatal period and infancy. A prominence of the left side of the chest had been noted in childhood but had apparently given rise to no symptoms. Nothing in his history suggested rheumatism or chorea. He completed elementary school and high school successfully and entered college, where, in 1932, he had some sort of acute febrile illness, which lasted only a few days. He was hospitalized for this period in the college infirmary, and then spent the next six months in bed at home and an additional six months in convalescence, apparently because continued weakness limited his activities. At some time during this illness tonsillectomy was performed.

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1 Lutembacher, R. De la stenose mitrale avec communication interauriculaire, *Arch d mal du coeur* **9** 237-260, 1916.

2 McGinn, S, and White, P D. Interauricular Septal Defect Associated with Mitral Stenosis, *Am Heart J* **9** 1-13 (Oct) 1933.

3 Geiger, A J, and Anderson, H C. Lutembacher's Syndrome Complicated by Acute Bacterial Endocarditis. Report of a Case Diagnosed During Life, *Am Heart J* **33** 240-249 (Feb) 1947.

In 1933 the patient undertook sedentary work and had no further disability until 1936, when he had an illness which, he said, was diagnosed as pleurisy, though the diagnosis seemed questionable. This illness was of short duration and did not require cessation of activity. The patient then remained well until Feb 28, 1942, when, while stepping down from a bus, he suddenly became weak and dyspneic and complained of palpitation. After hospitalization for fifteen days, he was able to return to work, but he continued to suffer from severe weakness, dyspnea and palpitation and could attend to his affairs only irregularly. In July 1942 he gave up work entirely. Shortly before he was examined at the Vicksburg Clinic, he had noticed swelling of the feet and enlargement of the abdomen, and he had again begun to suffer from dyspnea.

The patient was married and had two children, both of whom were living and well. His father had died at the age of 54 of a cerebral hemorrhage. His mother, three brothers and three sisters were living and well and were apparently normal in all respects.

Physical Examination—Examination on July 22, 1942 showed a fairly well developed man of asthenic habitus, in a rather poor state of nutrition. He was extremely pale, and his skin was *café au lait*. Cyanosis was insignificant. Dyspnea was severe. The veins of the neck were only slightly engorged, and the arteries in the neck showed no abnormal pulsation. The precordial region of the left side of the chest was extremely prominent as compared with the right side. Expansion was poor on the left side. The breath sounds were bronchial in character in the base of the right lung posteriorly. There were no rales and no evidence of fluid on either side of the chest.

The heart was enormously enlarged. The apex impulse, which was diffuse, was located in the left midaxillary line, 16 cm from the midline. The right border of dulness was 7 cm from the midline. Auscultation showed an overactive heart, with grossly irregular rhythm and periods of bigeminy and trigeminy. The first heart sound, which was increased in intensity, was followed by a loud systolic murmur (grade 4 plus). The second heart sound was rather impure. There was a middiastolic rumble. The blood pressure was 125 systolic and 70 diastolic.

The liver also was enormously enlarged. There was no peripheral edema.

The urine showed occasional leukocytic casts, even more occasional granular and hyaline casts and 15 to 20 red blood cells per high power field. Other routine laboratory studies revealed nothing abnormal. The roentgenogram of the chest (fig 1) revealed an enormous enlargement of both sides of the heart. The left border was prominent. There was relative absence of the aortic knob. The hilar shadows were prominent.

The electrocardiogram (fig 2) revealed auricular fibrillation, right axis deviation, ventricular premature beats with trigeminy and an intraventricular conduction defect.

The clinical diagnosis, on the basis of the history, physical findings and laboratory data, was rheumatic heart disease with mitral stenosis and auricular fibrillation.

Course of Illness—The patient was hospitalized from July 25 to Sept 15, 1942. Treatment, which was directed toward relief of congestive cardiac failure, included restriction of fluids and administration of diuretic drugs and of digitalis in adequate dosage. The effect of a high potassium-low sodium diet was also tested. Under this regimen the patient improved considerably, but on several occasions he had sudden paroxysms of rapid heart action, the rate rising to a maximum of 180 beats per minute, though it remained regular. An electrocardiogram taken during one

of these episodes revealed ventricular complexes of supraventricular origin, with the impulses arising near the junctional tissues. These attacks were of short duration, and were readily relieved by morphine.

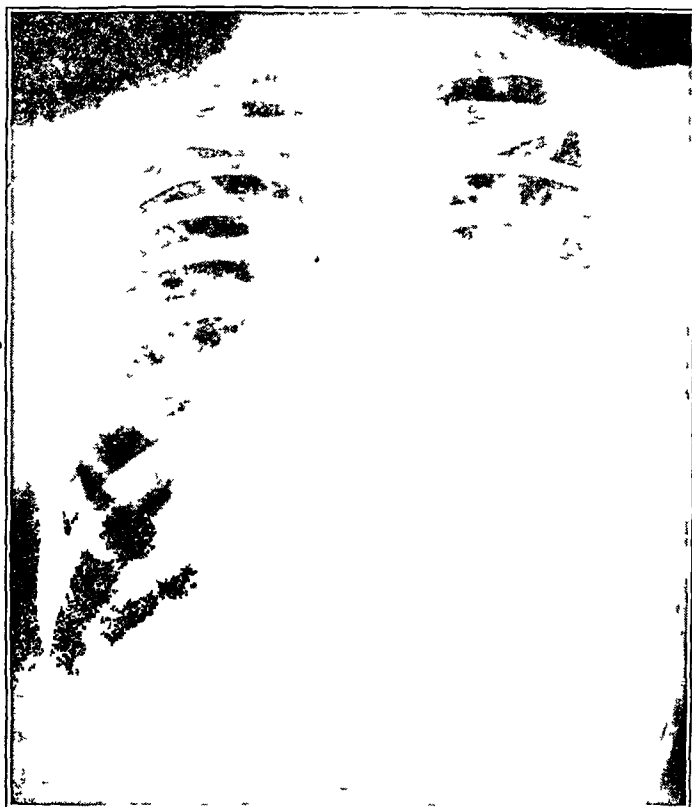


Fig 1—Roentgenogram of thorax (taken at 6 feet [180 cm]), showing enormous enlargement of heart to both right and left, prominent left border, hypoplastic aortic knob, basal pulmonary congestion and prominent hilar shadows

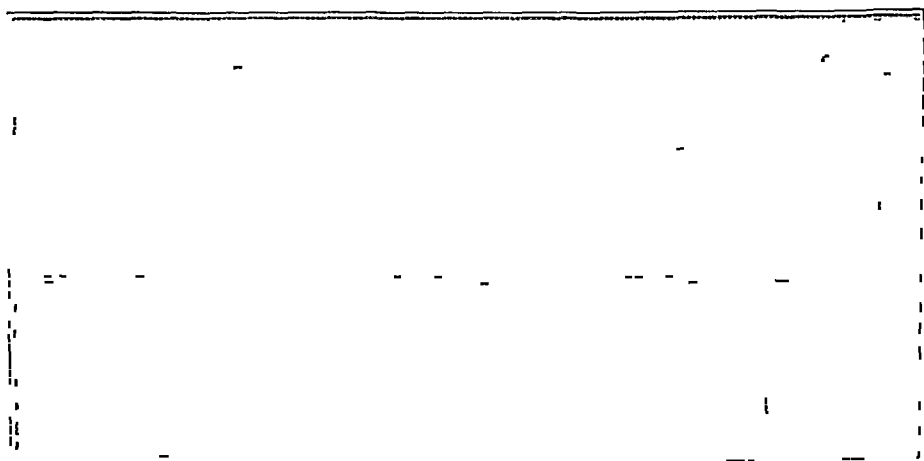


Fig 2—Electrocardiogram, showing auricular fibrillation, right axis deviation and intraventricular conduction defect

After his discharge from the hospital on Sept 15, 1942, the patient continued a bed and chair existence which constantly bordered on severe cardiac failure, in spite of the usual measures to prevent it. Frequent injections of mersalyl USP ("salyrgan") always produced effective diuresis and were not attended with unfavorable reactions.

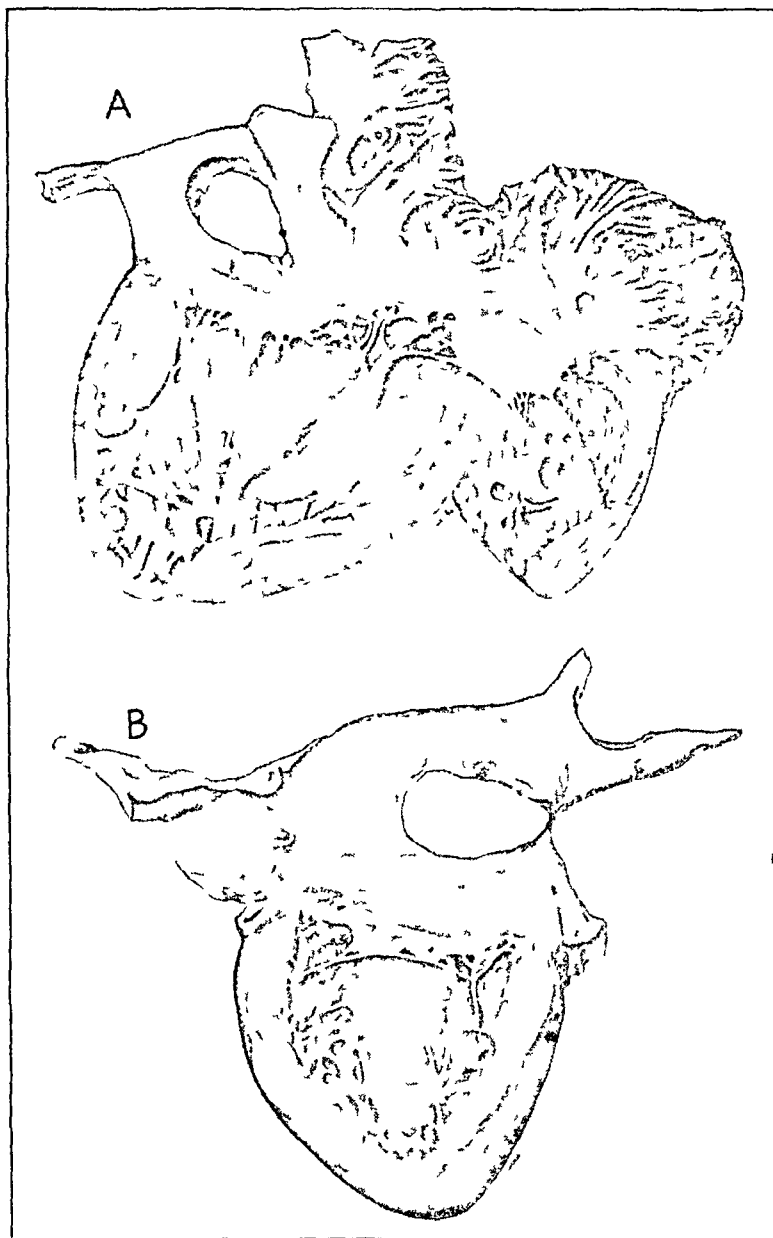


Fig 3—*A*, view of heart from right, after portions of huge right atrium were excised, showing large right ventricle and patent foramen ovale, with fimbriated margin, measuring 6 by 4 cm. *B*, view of heart from left, showing foramen ovale, roughened mitral valve and shortened chordae tendineae. Note disparity in size of the right and the left ventricle.

In July 1943 a pulmonary infarction developed, with severe pain in the chest and expectoration of bloody sputum. Thereafter the course of the illness was without special incident until Jan 1, 1944, when the usual signs of congestive cardiac failure again became pronounced. An ampul of mersalyl was given intravenously, without immediate reaction, and about an hour after it had been

administered the patient's wife left his room. When she returned shortly afterward, he was dead. The exact mechanism of death could not be determined, but, since the patient died soon after the injection of mersalyl, death was perhaps the result of ventricular fibrillation, which is the apparent cause of the occasional sudden deaths following the use of this drug.

Necropsy—The essential portions of the report of the necropsy, performed by Dr J C Henthorne, are as follows:

The body was thin and well developed. The left side of the chest was somewhat more prominent than the right. The peritoneal cavity contained no free fluid. There was approximately 500 cc of serous fluid in each pleural cavity. Fibrous adhesions were seen at the base of the right lung. The pericardial cavity contained about 1,000 cc of serous fluid.

The transverse diameter of the pericardial sac was 23 cm, the most striking feature of the enlargement being the size of the right atrium, which alone was about the size of a normal heart. The atrium measured 13 cm in transverse diameter, from the medial wall to the tip of the auricular appendix. It collapsed as soon as the heart was removed.

When the heart was opened, it was observed that hypertrophy of the right atrium and the right ventricle chiefly accounted for the cardiac hypertrophy. The right ventricle measured 11.5 by 9.5 by 3 cm. The wall was 0.7 cm thick. The collapsed right atrium, when it was opened, measured 10.5 by 10 by 11 cm. The columnae carnae and the papillary muscles were hypertrophied. The coronary sinus was dilated. The foramen ovale was patent (fig 3) and measured 6 by 4 cm. A remnant of fibrous membrane was attached to its border. Numerous thrombi were attached to the endocardium of the right auricular appendix.

The heart weighed 810 Gm. The aortic valve measured 6.6 cm and the mitral valve 10 cm. The free border of the mitral valve was thickened, and the chordae tendineae, attached to the posterior cusps, were thickened and shortened. The tricuspid valve measured 15.5 cm and the pulmonary valve 10 cm. The cavity of the left ventricle measured 10 by 6 by 4 cm, the wall was 1.2 cm thick. All valves except the mitral valve were normal in appearance, and the myocardium appeared normal.

There was slight atheromatous sclerosis of the coronary arteries. The pulmonary artery, which was greatly dilated, measured 4.5 cm in diameter.

The liver weighed 2,000 Gm. It was moderately congested, and its edge lay 7 cm below the costal margin. Careful examination of the spleen, kidneys, pancreas, adrenal glands, gastrointestinal tract, urinary bladder and prostate revealed no abnormalities.

COMMENT

The combination of abnormalities known as Lutembacher's syndrome was first recorded by Martineau in 1865 but was not fully described until Lutembacher's contribution, in 1916.

As already stated, small openings in the atrial septum, in the form of patent foramen ovale (patent ostium secundum), are the most frequent of all congenital cardiac defects. Defects larger than 1 cm in diameter, however, are not at all common. Roesler,⁴ in a complete review of the literature on the subject from 1826 to 1933, noted only

4 Roesler, H. Interatrial Septal Defect, *Arch Int Med* 54:339-380 (Sept) 1934.

61 such cases, to which he added a case of his own. In 30 of the 62 cases there was also a definite lesion of the mitral valve, and in 11 other cases a similar lesion was suspected. Not all the reports of the combined lesions included in Roesler's collection seem to be authoritative. McGinn and White,² in a critical review of the literature up to 1933, found only 23 instances of large atrial septal defect accompanied with mitral stenosis, and autopsy figures suggest that the smaller number is more likely to be correct. Traum⁵ found only a single instance of Lutembacher's syndrome listed in 700 necropsy reports filed in the Veterans' Hospital Cardiac Research Unit, and only 2 instances were identified in 6,800 postmortem examinations at the Massachusetts General Hospital.²

Large atrial septal defects have been observed almost exclusively in women. In the 23 cases collected from the literature by McGinn and White² only 1 of the patients was a man, their own patient, like the patient in the case recorded in this communication, was a man.

Pathogenesis—Atrial septal defects are the result of failure of development and fusion of three structures: (1) the endocardial cushions, (2) the septum primum and (3) the septum secundum.⁶ In the normal course of embryonic development a primary septum grows downward from the superior and posterior portions of the (then) single atrial cavity to meet the endocardial cushions, which develop from the inferior portion of the (then) single atrium. The fusion of these two structures obliterates the ostium primum, the primary communication between the two atria. If there is failure of fusion, the result is the defect known as persistent ostium primum. Later an opening, the foramen ovale, or ostium secundum, is formed in the primary septum, and still later a septum secundum is formed to the right of the foramen ovale. In the normal course of development, the foramen ovale is closed by the fusion of these two septums at birth or soon afterward. If there is failure of fusion, the result is the defect known as persistent ostium secundum, or patent foramen ovale.

There are at least three theories of the relation of the atrial septal defect to mitral stenosis in Lutembacher's syndrome. Lutembacher¹ himself stated the belief that the mitral stenosis was congenital and was the primary defect, his theory being that the increase of pressure, caused by the stenosis, within the left atrium prevents closure of the septum. Von Rokitansky⁷ advanced the theory that hypoplasia of the aorta, which is usually present in this syndrome, is the primary cause of septal failure.

5 Traum, A. H. Interauricular Septal Defect with Mitral Stenosis—Lutembacher's Syndrome, *M. Bull. Vet. Admin.* **20** 274-276 (Jan.) 1944.

6 Tinney, W. S., and Barnes, A. S. Interauricular Septal Defects, *Minnesota Med.* **25** 637-643 (Aug.) 1942.

7 Von Rokitansky, cited by Roesler.⁴

His reasoning was that when hypoplasia of the aorta is present increased pressure in the left side of the heart prevents closure of the atrial septum. The fallacy in this reasoning is that such defects of the atrial septum do not occur in congenital aortic stenosis or atresia.

Most authorities accept neither Lutembacher's nor von Rokitsansky's theory but regard the mitral stenosis as an acquired rheumatic lesion.⁸ This theory is supported by the fact that in a quarter of the cases of large atrial septal defects on record no accompanying mitral stenosis was noted. It is probable that in this, as in other cardiac lesions, minor congenital defects in the mitral valve make it more susceptible to a rheumatic process. The frequent occurrence of auricular fibrillation in cases of Lutembacher's syndrome favors the concept of an acquired rheumatic lesion of the mitral valve, though against the theory is the fact that a positive history of rheumatic infection was obtained in only 3 of the 24 cases collected by McGinn and White,² including their own. It was present in the case reported by Geiger and Anderson,³ but not in the case reported in this communication.

Anatomic Lesion—Large atrial septal defects are usually single, though not infrequently the margins show fenestration. The defect is usually oval, and the diameter in the cases recorded to date has varied from 1.0 to 5.5 cm.⁴ The heart is usually globular, and the enlargement is often enormous. It is chiefly the result of hypertrophy of the right auricle and the right ventricle, both of which are likely to be tremendously dilated. Recorded cardiac weights have varied from 250 to 1,035 Gm.⁴ The pulmonary artery is greatly dilated, and the aorta is usually hypoplastic. The accompanying defect of the mitral valve may vary from slight roughening of the cusps to such extreme stenosis that only a minute orifice remains. In the case recorded here, the patent foramen ovale measured 6 by 4 cm., the defect being apparently larger than any previously observed.

Clinical Picture—The presenting symptoms and signs in Lutembacher's syndrome are usually breathlessness, peripheral edema, palpitation and cough. In other words, the clinical picture is suggestive of congestive cardiac failure. Patients afflicted with this anomaly are usually described as being of delicate or of asthenic habitus. They frequently present a prominent deformity of the precordium, with bulging on the left. Cyanosis is uncommon except as a terminal event, when the admixture of venous with arterial blood reaches 33 per cent. Clubbing of the fingers is also uncommon. The clinical observations in the case recorded here were generally those described.

The cardiac rhythm may be normal, though premature beats are common, and auricular fibrillation, as in this case, is likely to occur at

8 McGinn and White² Roesler⁴

some time in the course of the disease. The presystolic murmur typical of mitral stenosis is the predominant finding in most cases, though sometimes no murmurs at all, or only a systolic murmur, can be detected. In patients with fibrillation, as in this instance, the middiastolic rumble of mitral stenosis may be heard. It must be remembered, however, that such a rumble may be heard, even when mitral stenosis is absent, as the result of the passage of blood through the hardened, calcified or fenestrated margins of the patent foramen ovale. When an apical thrill is present, which is frequent, it corresponds in time with the more prominent murmur present. The blood pressure is usually within normal range. Paroxysmal ventricular tachycardia, as in this case, is relatively common and no doubt bears a causal relation to the sudden death often observed in this condition. Subacute bacterial endocarditis, although common with other congenital cardiac lesions, is unusual with Lutembacher's syndrome.⁹

Roentgenographic and Electrocardiographic Findings—The majority of writers agree that the diagnosis of Lutembacher's syndrome, though it may be suspected on the basis of clinical manifestations,¹⁰ is almost never justified without roentgenographic confirmation. The roentgenogram of the thorax is characteristic.¹¹ The heart appears globular and is likely to be enormously enlarged in all directions (fig 1). Roesler⁴ stated that four other factors are necessary for diagnosis: (1) an enlarged pulmonary conus, (2) extensive hypertrophy of the right side, (3) wide hilar shadows and (4) a diminished aortic knob. Fluoroscopic examination confirms the roentgenographic findings and may occasionally reveal calcification in the mitral valve or in the annulus fibrosus.

The large shadows in the hilus (fig 1), which Roesler⁴ regarded as necessary for a diagnosis of Lutembacher's syndrome, have occasionally been mistaken for lymph nodes, and even for tumors. Two patients, in fact, were subjected to exploratory operation for a possible pulmonary neoplasm.^{11c}

As in cases of most other congenital cardiac defects, there is nothing pathognomonic about the electrocardiographic findings in cases of Lutembacher's syndrome. In view of the presence of two anatomic

⁹ McGinn and White² Geiger and Anderson³ Tinney and Barnes⁶

¹⁰ (a) McGinn and White² (b) Bedford, D. E. Papp, C., and Parkinson, J. Atrial Septal Defect, *Brit Heart J* **3** 37-68 (Jan) 1941

¹¹ (a) McGinn and White² (b) Tinney and Barnes⁶ (c) Bavin, G. J. Patent Interauricular Septum Associated with Mitral Stenosis. Lutembacher's Syndrome, *Radiology* **38** 1-6 (Jan) 1942 (d) Masters, A. M. *The Electrocardiogram and X-Ray Configuration of the Heart*, ed 2, Philadelphia, Lea & Febiger, 1942

defects which cause enlargement of the right side of the heart, one might expect to find greater right axis deviation than would be present with atrial septal defects alone. This is not always true. Right axis deviation is common,¹² but is also frequently absent. It was present in only 1 of the 9 cases of large atrial septal defects reported by Schnitker.¹³ While its presence may be a confirmatory sign of Lutembacher's syndrome, its absence does not exclude the diagnosis.

Because of the great hypertrophy and dilatation of the right atrium, the large P waves frequently seen in leads I and II in cases of Lutembacher's syndrome are not unexpected. The waves are frequently notched and bear no direct relation to the degree of atrial enlargement. Abnormal forms of the QRS complex are common, as are biphasic QRS complexes of the type often associated with extreme hypertension. Intraventricular conduction defects are common. There are no significant changes in the T waves.

Auricular fibrillation is frequent with Lutembacher's syndrome,⁶ although it is not usually encountered in other types of congenital cardiac disease. It is also seldom seen in patients under 50 years of age having atrial septal defects without concomitant mitral stenosis. The extreme dilatation of the auricles is an important factor in the causation of the disturbed rhythm.

Prognosis—Patients with Lutembacher's syndrome are often capable of a surprising amount of physical exertion. Firket's¹⁴ patient passed successfully through eleven pregnancies and three abortions and lived to the age of 74 years. One of Lutembacher's own patients was 61 years of age and had had seven pregnancies without evidence of cardiac failure. Bonnabel's¹⁵ 2 patients were 62 and 74 years of age, respectively. Erickson and Willius,¹⁶ who stated that the average duration of life in patients with large atrial septal defect is only 32.5 years, themselves reported a case in which the patient lived to be 68 years old.

Lutembacher's syndrome is therefore not incompatible with a relatively long span of life. On the other hand, the prognosis in these cases is uncertain, and death is likely to occur, usually rather suddenly, at or near 35 years of age, as in the case recorded in this communication.

12 Roesler, H.⁴ Bedford, Papp and Parkinson.^{10b}

13 Schnitker, M. A. *The Electrocardiogram in Congenital Cardiac Disease*, Cambridge, Mass., Harvard University Press, 1940.

14 Firket, cited by White.¹⁷

15 Bonnabel, J. *Contribution a l'etude de quelques affections congenitales du coeur compatibles avec l'existence et de leur pronostic*, Thesis, Paris, 1906, no. 39.

16 Erickson, C. W., and Willius, F. A. *Cardiac Clinics. Cardiopathy of Undetermined Origin. Enormous Cardiac Enlargement, Recurrent Congestive Failure, Heart Block, and Cerebral Embolism, Clinical and Postmortem Findings*, Proc. Staff Meet., Mayo Clin. **11** 248-253 (April 15) 1936.

One possible explanation for the prolongation of life is that the septal defect somewhat relieves the burden imposed on the pulmonary circulation and on the right side of the heart by the presence of mitral stenosis¹⁷

SUMMARY

The case of Lutembacher's syndrome (large atrial septal defect with concomitant mitral stenosis) described in this communication has been put on record because the septal defect is apparently the largest yet to be reported. The diagnosis in this case was not made ante mortem, although in retrospect it is evident that the patient presented all the important phenomena characteristic of this condition.

Vicksburg Clinic

¹⁷ White, P. D. Heart Disease, ed 2, New York, The Macmillan Company, 1937

RENAL INSUFFICIENCY DUE TO PAROXYSMAL COLD HEMOGLOBINURIA

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AND

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PAROXYSMAL cold hemoglobinuria due to destruction of red cells has been regarded as a troublesome though nonfatal result of syphilis. Its rarity is reflected in the report of Thurmon and Blain, who noted its occurrence in 1 of 17,300 patients admitted to the Massachusetts General Hospital.¹ While late congenital syphilis claims the larger number of victims, acquired syphilis in the tertiary stage accounts for a noteworthy fraction of the cases.

The clinical syndrome may be suspected when malaise, myalgia, headache and abdominal cramps are climaxed by a severe shaking chill reminiscent of a malarial rigor occurring from several minutes to hours after exposure to cold. Fever usually follows these events and lasts for an hour or two. When intravascular hemolysis is sufficiently severe, free hemoglobin traverses the glomerular filter and appears in the urine for a variable length of time depending on the severity of the hemolytic episode. Persisting abdominal cramps or Raynaud's phenomena are a token of the extensive vasoconstriction which takes place. Sometimes urticaria plays a dominant part in the symptomatology. The patients are depleted and often anemic after a hemolytic attack.

Since it is the rule for patients to recover from such episodes and remain in a state of health reflecting only the other accompaniments of late syphilis, a case in which renal insufficiency terminated fatally should be of interest because of its rarity. In addition, some of the problems posed by this report may have a bearing on the course and prognosis of kindred ailments, such as the necrotizing renal processes following mismatched transfusion and crush injury.

Associate attending physician (Dr. Sussman) and assistant, Cardiovascular Research Unit (Dr. Kayden), Medical Service of Beth Israel Hospital.

1 Thurmon, F., and Blain, D. Paroxysmal Hemoglobinuria, Observations Based upon Study of Three Cases, *Am J Syph* **15** 350-367, 1931. Mackenzie, G. H. Paroxysmal Hemoglobinuria, *Medicine* **8** 159-191, 1929.

REPORT OF A CASE

W E, a 56 year old married Negro porter, entered the hospital on Jan 14, 1944, because of passage of "reddish urine" five days before. He reported having had eleven similar episodes in the past two years with a similar clinical pattern.

After exposure to cold weather, the patient was seized with a severe shaking chill accompanied by pain in the lower part of the back and the legs, followed by a desire to urinate. This usually resulted in the passage of bright or dark red urine, followed by fever and ringing in the ears. These symptoms ordinarily lasted half a day or less. After each attack the urine returned to a normal color and the patient was undisturbed until the succeeding attack. Spring and summer seizures never occurred.

The last episode occurred on Jan 9, 1944, after prolonged exposure to cold. This attack was extraordinarily severe and lasted a longer time than previous seizures. Pain in the lumbar region was prominent from the onset to the time of the patient's admission to the hospital.

Despite an adequate fluid intake, the urinary output had been meager, though the red color had disappeared since the day of the attack. For four days before his entrance to the hospital, and for the first time in his life, the patient was distressed because of shortness of breath. Several small hemoptyses accompanying a cough had also occurred two days before admission.

His past history disclosed a gonorrheal infection in 1918 and a chancre, apparently syphilitic, in August of 1937. Antisyphilitic treatment was administered for two and a half years (October 1937 to March 1940) so that a total of twenty-eight arsphenamine, twenty mercury and eighteen bismuth injections was given. During October of 1938, the Wassermann reaction was reported as 4 plus. In March 1939 the reaction to the Kline test was 3 plus, and in February 1940 it was 4 plus. In 1942 the reaction to the Kahn test was positive.

In 1940 the discharge diagnosis at another hospital was latent syphilis and hypertension. An insurance policy requiring a physical examination was granted in 1943. In January 1944, three days prior to admission, the patient was seen at this hospital's clinic and the blood pressure was 128 systolic and 84 diastolic. When he was admitted the physical examination revealed no abnormalities except in the chest. Dry rales were audible at the bases of both lungs. The heart sounds were of good quality, a soft systolic murmur was audible at the apex and the aortic second sound was accentuated. The heart was not enlarged on fluoroscopic examination. The blood pressure was 200 systolic and 110 diastolic.

Laboratory Data—The urine had a specific gravity of 1.012 and was cloudy. It gave a 1 plus reaction for albumin and contained no glucose or acetone. The reaction to the benzidine test was positive. Microscopic examination showed many clumped white cells, many red cells and many red blood cell and granular casts. The red blood cell count was 2,500,000, hemoglobin content 8.5 Gm (55 per cent), and the white blood cell count 9,400. The differential count showed 5 staff forms, 79 segmented forms, 14 small lymphocytes and 2 monocytes. The icterus index was 6.3 and the serum bilirubin content 0.20 mg per hundred cubic centimeters. The carbon dioxide content was 29 volumes, nonprotein nitrogen 13.6 mg, calcium 8.8 mg and whole blood chloride as sodium chloride 540 mg, per hundred cubic centimeters. The plasma protein measured 7.08 Gm per hundred cubic centimeters, with 4.09 Gm of albumin and 2.99 Gm of globulin (ratio of 1.37). Spectroscopic examination of the blood serum revealed the presence of hemoglobin. The Wassermann, Kahn and Kline reactions were all positive.

The diagnosis was (1) paroxysmal cold hemoglobinuria due to syphilis resulting in hemoglobinuric nephrosis and azotemia and (2) hypertensive arteriosclerotic heart disease with left ventricular failure

Course in the Hospital—A large fluid intake was provided by mouth and was supplemented by the intravenous administration of Hartmann's solution (one-sixth molar sodium lactate) Administration of potassium bicarbonate (2 Gm four times a day) was started on the second day in the hospital (32 Gm in all given) Under this regimen the urinary output rose from 750 cc on the second day in the hospital to 2,300 cc on the fifth day The urine was now alkaline (p_H 7.5) The carbon dioxide content rose to 42.6 volumes per cent, but the nonprotein nitrogen level rose to 158 and then to 171 mg per hundred cubic centimeters The urine remained clear, the specific gravity never rising above 1.010 The patient was troubled with considerable abdominal distention, which responded poorly to the frequent use of neostigmine and enemas An electrocardiogram taken on January 18 showed decided left deviation of the electrical axis and intraventricular block, the QRS interval measured 0.12 second On the same day the Donath-Landsteiner test gave a negative reaction Sternal marrow aspirated was normal The blood pressures were as follows on January 15, 174 systolic and 96 diastolic, on January 17, 174 systolic and 87 diastolic, on January 18, 192 systolic and 84 diastolic

On the evening of the fifth day in the hospital the patient became severely dyspneic and orthopneic, and moist rales were audible in both pulmonary fields The usual treatment for acute left ventricular failure with pulmonary edema was instituted, including the use of morphine and rapid digitalization Despite this therapy, the patient died on the morning of the sixth day

Postmortem Examination—Postmortem examination was performed by Dr Alfred Plaut The significant observations were limited to the heart, lungs and kidneys The heart weighed 480 Gm, the thickness of the left ventricular wall was 22 mm and that of the right ventricular wall 8 mm The left auricle and ventricle appeared dilated The aorta showed moderate arteriosclerotic involvement There was no evidence of syphilis The lungs were heavy and contained considerable bloody and foamy fluid on the cut surface The right kidney weighed 275 Gm and the left 270 Gm They were large and heavy, and their capsules stripped with difficulty The cortex was thick and stained a light brownish red

Microscopic Report—The microscopic report on the kidneys was as follows While the number of glomeruli is decreased, most of them are normal Some, however, exhibit varying degrees of shrinking, and their capsules are thickened The capsular spaces throughout are empty There is moderate diffuse fibrosis throughout the kidney Areas of more intense fibrosis correspond to those areas in which many tubules are atrophic The contour of the capsule is somewhat undulating, and there are numerous shallow scars These scars contain many cells, mostly mononuclear The majority of these cells are larger than lymphocytes, but there are also many typical lymphocytes

Except for slight elastosis, which is not unusual at the age of 56, no changes in the blood vessels are detected There is no pyelitis nor any ascending inflammation The hilar fat is infiltrated in places with small round cells and large mononuclear elements with rather compact protoplasm One small hemorrhage is situated near the tip of a pyramid There is no diffuse inflammatory process

The primary convoluted tubules are moderately wide Their lumens contain some indistinct amorphous material The epithelium of the convoluted tubules contains little fat



Fig 1—*A*, low power view demonstrating collecting tubule filled with pigment and cellular debris and inflammatory focus of round cells and leukocytes, *B*, high power magnification of collecting tubule, *C*, high power magnification of inflammatory focus

Brownish masses, some amorphous, some finely or coarsely granular and some of larger particles, occupy the lumens of many collecting tubules, of some of Henle's loops and of many distal convoluted tubules. While these masses occasionally resemble erythrocytes in size and shape, they all stain differently from the red blood cells in blood vessels. In spite of continued search, no red blood cells can be demonstrated in the lumens of any renal tubule. In some tubules the lumen is filled with brown masses while the epithelium appears intact, in some the lumen is free and the intact-appearing epithelium is filled with pigment granules and in some the epithelial cells contain pigment granules but their outlines are much distorted. In other tubules the epithelium appears almost entirely destroyed and only the pigment is visible. All gradations among these different phases can be found. There also is an alternation of normal-appearing and of obviously diseased granular epithelial cells in cross sections of tubules in which no pigment is seen.

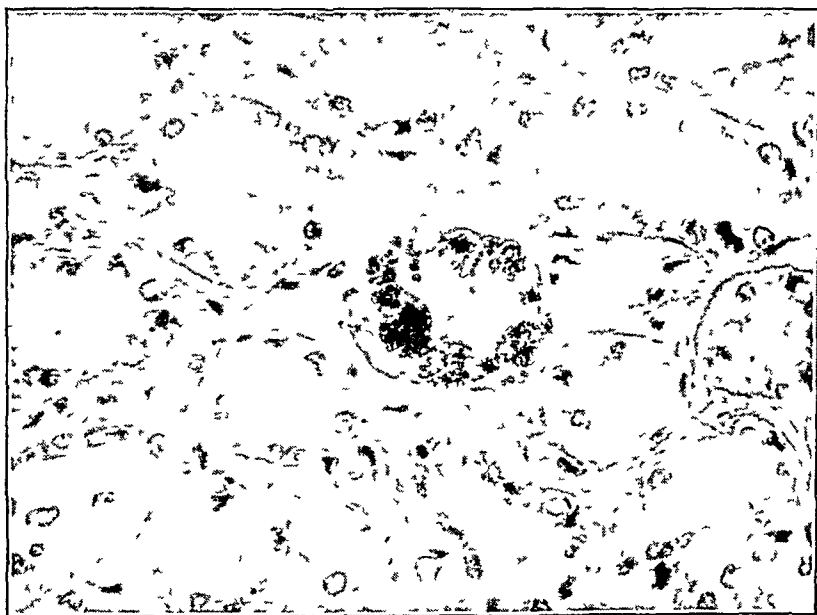


Fig 2—View showing many tubules. The center one has pigment granules within an epithelial cell, and cell outlines are much distorted. Above it is a regenerating tubule, below it are several tubules with necrotic epithelium.

The color of the pigment varies from a deep brown to a pale yellowish green. The lighter shades, however, are only seen in the small granules. All the thicker masses appear dark brownish. Independent of the pigment masses, hyaline casts are found, some of which appear pink in the sudan stain.

Inflammatory foci are numerous, in many of these foci a damaged tubule can be recognized in the center. These tubules contain pigment as described. Various degrees of destruction are seen, and in some foci no remnants of the tubules are recognizable. The ratio of leukocytes and mononuclear elements varies. Leukocytes also are present in the lumen of the tubules, generally mingled with masses of pigment and desquamated epithelium. Occasionally, tubules are seen obviously in the process of destruction, but there is no inflammatory reaction in their neighborhood. The inflammatory foci reach 2 mm in diameter. Small calcific foci are present.

Iron Reaction The iron reaction (prussian blue) of the glomeruli, the inflammatory foci and the interstitial tissue is negative. The loose masses in the lumen of the primary convoluted tubules give a rather faint iron reaction. The reaction of the pigment masses in the epithelium of the loops of Henle and in the secondary convoluted tubules is strongly positive. The reaction of the masses in the lumen of the large collecting tubules again are positive.

COMMENT

A Cause for the Negative Donath-Landsteiner Reaction—That this case represents the syndrome of paroxysmal cold hemoglobinuria is apparent from the clinical history, although the Donath-Landsteiner reaction was negative. This reaction is based on the presence of a cold hemolysin circulating in the plasma. If red cells of the same group are added to the plasma containing this hemolysin and the mixture is chilled in ice water and then reheated in the presence of complement, hemolysis occurs. In the performance of the test, only the patient's hemolysin-laden plasma need be used. In the presence of guinea pig complement and any red blood cells of the same blood group, the red blood cells will be hemolyzed. Two stages characterize the hemolytic process. The first is cold fixation of the hemolysin on the erythrocyte at appropriately low temperatures, for which action complement is unnecessary. The second is heat lysis of the already sensitized erythrocytes after they are warmed to 37 C in the presence of complement. A common identity for this reaction and the Wassermann reaction has been suggested but has been disproved by cold-fixing all the hemolysin in a given blood sample and observing no change in the titer in a subsequently performed Wassermann test, despite the fact that the Donath-Landsteiner reaction becomes negative.

The absorption of all the hemolysin in the cold may well be the explanation of the negative Donath-Landsteiner reaction in this instance, for according to the patient's history this was the most severe and prolonged exposure of the twelve which he had suffered. The severity of the subsequent hemolytic reaction strengthens the conclusion that all the hemolysin was absorbed by the lysed erythrocytes, which left none available in the plasma.² The Rosenbach test, in which the patient's feet are immersed in ice water for ten minutes and hemolysis is awaited, was considered a dangerous procedure, although the modification known as the Ehrlich test might have been carried out. In this test localized hemolysis is produced in a finger by arresting venous return with a ligature tied at the base of the finger and immersing the finger in ice water. The presence of free hemoglobin in the heated serum collected from the chilled digit documents a hemolytic reaction occurring in the cold.

² Rosen, S F Paroxysmal Hemoglobinuria with Case Report, South M J
26 1038-1044, 1933

Since all these tests depend on the availability of cold hemolysin, it is likely that none of them would have been helpful in identifying the cause of the hemoglobinuria because of the probable absorption of all the available hemolysin

B Relation to Post-Transfusion and Crush Injury Nephrosis—The manner in which this patient died with evidence of renal insufficiency reveals an arresting similarity to post-transfusion renal reactions which occur after large quantities of incompatible blood have been injected. The precise mechanism by which hemoglobin damages the kidney in these instances has engaged the attention of numerous investigators.³ The result of their studies indicates that the healthy kidney is well able to cope with free hemoglobin when the plasma level is low, in which instance it behaves like other threshold substances, traversing the glomerular filter and then undergoing reabsorption in the tubule and not appearing in the urine.⁴ Such a state of affairs apparently exists up to levels of 135 mg of hemoglobin per hundred cubic centimeters of plasma.⁵ When the hemoglobin leaves the erythrocytes and attains a plasma level in excess of 135 mg, it is excreted in the urine because the tubular capacity for hemoglobin reabsorption has been reached and the tubule cells are incapable of handling increased amounts of that protein delivered in the glomerular filtrate. An interesting observation on the threshold level of hemoglobin reveals that once the tubular cells are loaded with iron pigment their continued ability to reabsorb hemoglobin is diminished and is reflected by a fall in

3 (a) Baker, S. L., and Dodds, E. C. Obstruction of the Renal Tubules During Excretion of Hemoglobin, *Brit J Exper Path* **6** 247-260, 1925. (b) De Gowing, E. L., Warner, E. D., and Randall, W. L. Renal Insufficiency from Blood Transfusions. Anatomic Changes in Man Compared with Those in Dogs with Experimental Hemoglobinuria, *Arch Int Med* **61** 609-630 (April) 1938. (c) De Navasquez, S. Excretion of Haemoglobin, with Special Reference to "Transfusion" Kidney, *J Path & Bact* **51** 413-425, 1940. (d) Foy, H., Altman, A., Barnes, H. D., and Kandi, A. Anuria, with Special Reference to Renal Failure in Blackwater Fever, Incompatible Transfusions, and Crush Injuries, *Tr Roy Soc Trop Med & Hyg* **36** 197-238, 1943. (e) Flink, E. B. Blood Transfusion Studies. III. The Relationship of Hemoglobinemia and of the p_H of the Urine to Renal Damage Produced by Injection of Hemoglobin Solutions into Dogs, *J Lab & Clin Med* **32** 223-261, 1947. (f) Goldring, W., and Graef, I. Nephrosis with Uremia Following Transfusion with Incompatible Blood. Report of Seven Cases with Three Deaths, *Arch Int Med* **58** 825-845 (Nov) 1936.

4 Ottenberg, R., and Fox, C. L., Jr. The Rate of Removal of Hemoglobin from the Circulation and the Renal Threshold in Human Beings, *Am J Physiol* **123** 516-525, 1938.

5 Gilligan, D. H., Altschule, M. D., and Katersky, E. M. Studies of Hemoglobinemia and Hemoglobinuria Produced in Man by Intravenous Injection of Hemoglobin Solutions, *J Clin Investigation* **20** 177-187, 1941.

the renal threshold of hemoglobin by as much as 60 per cent⁶. Thus, repeated episodes of hemoglobinemia occurring at short intervals are more apt to be attended by hemoglobinuria than is an initial episode of more extensive intravascular hemolysis. That the height of the hemoglobin level attained in the plasma is the chief factor in determining renal insufficiency is indicated by the recent report of Flink,^{3e} who observed serious renal insufficiency in all dogs in which the plasma values for hemoglobin exceeded 37 Gm per hundred cubic centimeters immediately after completion of the injection of hemoglobin. Similarly, Foy and Kondi⁷ observed oliguria and anuria in human beings with the highest levels of plasma hemoglobin during blackwater fever.

It is surprising that the giant size of the hemoglobin molecule (68,000) is not an absolute deterrent to its passage through the glomerular filter, its clearance is 3 per cent of that of creatinine, a substance which in the dog is a measure of glomerular filtration since it is not reabsorbed by the tubules. Lichty, Havill and Whipple^{6e} suggested that only 3 per cent of the glomerular pores are large enough to permit the passage of this large hemoglobin molecule. The appearance of methemalbumin⁸ a highly toxic substance, in the plasma, is the herald of extensive hemolysis and is indicative of plasma hemoglobin levels in the neighborhood of 300 to 500 mg per hundred cubic centimeters.

Myoglobin, another protein closely related to hemoglobin, whose molecular weight is only one-fourth (17,500) that of the latter, is observed in the urine of persons dying of renal insufficiency as a result of muscle destruction, with a clinical and pathologic picture often indistinguishable from the renal necrosis resulting from mismatched transfusion.

6 (a) Yuile, C. L. Hemoglobinuria, *Physiol Rev* **22** 19-31, 1942. (b) Monke, J. V., and Yuile, C. L. Renal Clearance of Hemoglobin in Dog, *J Exper Med* **72** 149-165, 1940. (c) Bogniard, R. P., and Whipple, G. H. Iron Content of Blood Free Tissues and Viscera. Variations Due to Diet, Anemia and Hemoglobin Injections, *ibid* **55** 653-665, 1932. (d) Yuile, C. L., Steinman, J. F., Hahn, P. F., and Clark, W. F. The Tubular Factor in Renal Hemoglobin Excretion, *ibid* **74** 197-202, 1941. (e) Lichty, J. A., Jr., Havill, W. H., and Whipple, G. H. Renal Thresholds for Hemoglobin in Dogs. Depression of Threshold Due to Frequent Hemoglobin Injections and Recovery During New Periods, *ibid* **55** 603-615, 1932.

7 Foy, H., and Kondi, A. Blackwater Fever in Macedonia, *Tr Roy Soc Trop Med & Hyg* **31** 123-138, 1937, Spectroscopic Analysis of Pigments in Serum and Urines of Blackwater Fever, *ibid* **32** 49-65, 1938.

8 Fairley, N. H., and Bromfield, R. J. Laboratory Studies in Malaria and Blackwater Fever. New Blood Pigment in Blackwater Fever and Other Biochemical Observations, *Tr Roy Soc Trop Med & Hyg* **28** 307-334, 1934.

The recent air war enabled the British to study cases of crush injury and myoglobinuria with great care. It is significant that most of the deaths occurred on the sixth day following injury, after signs of shock had disappeared, and usually climaxed progressive renal impairment during which blood pressures rose and azotemia developed. Observations on the renal insufficiency following transfusions are strikingly similar since most of the reported deaths occurred seven to ten days after the initiating hemolytic accident.

Trauma is unnecessary for the production of the syndrome, since Haff disease,⁹ cases of which were reported from Königsberg, and acute paralytic myoglobinuria¹⁰ may produce completely similar clinical patterns.

During the onset of crush injury,¹¹ the urine is generally highly acidic, with a p_H of 4.5, containing acid hematin crystals. As time goes on, fixation of the specific gravity occurs despite the presence of a diminishing urinary volume. An inverse ratio between the urea and the chloride in the plasma and blood is observed, the urea content being high in the plasma and the chloride content low. Potassium and creatinine levels are high in the initial urine voided. The fatalities occurring are suggestive of fatal potassium poisoning, with death from cardiac impairment, since the electrocardiogram discloses increased height of the T waves and disturbances in intraventricular conduction.

C Elements Producing Renal Tubular Necrosis (Experimental Observations)—Experimental studies are helpful in analyzing the mechanism of tubular injury in these instances. Important among them is the work of Yuile and others,¹² who showed that ischemia or previous tartrate injury rendered the renal tubules of rabbits more susceptible to destruction. It should be recalled that in 1937 Fishberg stressed the basic nature of the diminished circulating blood volume and the decreased renal blood flow as a cause of the renal impairment accompanying prerenal azotemia in a great variety of circumstances.¹³ Since that

9 Ross, J. F. *Medical Progress: Hemoglobinemia and the Hemoglobinurias*, New England J. Med. **233**: 766, 1945.

10 Bywaters, E. G. L., and Dible, J. H. *Acute Paralytic Myohaemoglobinuria in Man*, J. Path. & Bact. **55**: 7-15, 1943.

11 Bywaters, E. G. L., and Beall, D. *Crush Injuries with Impairment of Renal Function*, Brit. M. J. **1**: 427-432, 1940. Bywaters, E. G. L. *Ischemic Muscle Necrosis: Crushing Injury, Traumatic Edema, Crush Syndrome, Traumatic Anuria, Compression Syndrome, a Type of Injury Seen in Air Raid Casualties Following Burial Beneath Débris*, J. A. M. A. **124**: 1103-1109 (April 15) 1944.

12 Yuile, C. L., Gold, M. A., and Hinds, E. S. *Hemoglobin Precipitation in Renal Tubules: A Study of Its Causes and Effects*, J. Exper. Med. **82**: 361-374, 1945.

time it has been recognized that during shock, hemorrhage and vasoconstriction renal necrosis may occur without the intervention of any other mechanism, being solely a result of tubular anoxia¹⁴

Trueta and his colleagues¹⁵ have recently demonstrated how renal cortical blood flow may be short-circuited by neural impulses in the rabbit, producing an almost pure subcortical or medullary renal circulation with consequent decrease in glomerular filtration and impaired tubular function. These were evidenced by oliguria and the arterial quality of the bright red blood entering the renal vein. Similarly, widespread vasoconstriction which occurs in the course of posthemorrhagic, postoperative and posthemolytic states is associated with a decrease in circulating blood volume and diminished renal blood flow leading to tubular anoxia which is evidenced by oliguria and often anuria. An element of tubular anoxia is thus seen to be an integral part of the renal impairment accompanying transfusion reaction and crush injury.

Smith's¹⁶ suggestion that the reabsorption of water is divided into obligatory and facultative areas of the renal tubular apparatus completes the explanation for the mechanism of injury in hemoglobinuric necrosis. According to his view, which is based on the studies of Walker and others¹⁷ Shannon¹⁸ and Verney,¹⁹ 85 per cent of the glomerular filtrate is reabsorbed in the proximal tubular segment of the nephron, whereas 15 per cent is the responsibility of the distal tubule and the thin limb of Henle's loop under the influence of the antidiuretic hormone of the neurohypophysis. The concentrating activity which creates a hypertonic urine apparently resides in the lower nephron.

It is during the early phases of hemoglobin excretion, while there is still functional tubular integrity, that this concentrating process

13 Fishberg, A. M. Prerenal Azotemia and Pathology of Renal Blood Flow, *Bull. New York Acad. Med.* **13** 710-732, 1937.

14 Macgraith, B. G., Havard, R. E., and Parsons, D. S. Renal Syndrome of Wide Distribution Induced Possibly by Renal Anoxia, *Lancet* **2** 293-296, 1945.
Tomb, J. W. Anuria and Anoxia, *J. Trop. Med.* **45** 125, 1942.

15 Trueta, J., Daniel, P., Barclay, A. E., Franklin, K. S., and Prichard, M. M. L. Renal Pathology in the Light of Recent Neurovascular Studies. Preliminary Communication, *Lancet* **2** 237-238, 1946.

16 Smith, H. W. The Excretion of Water, *Bull. New York Acad. Med.* **23** 177-195, 1947.

17 Walker, A. M., Bott, P. A., Oliver, J., and MacDowell, M. C. Collection and Analysis of Fluid from Single Nephrons of Mammalian Kidney, *Am. J. Physiol.* **134** 580-595, 1941.

18 Shannon, J. A. Control of Renal Excretion of Water. Effect of Variations in State of Hydration on Water Excretion in Dogs with Diabetes Insipidus, *J. Exper. Med.* **76** 371-386, 1942.

19 Verney, E. B. Absorption and Excretion of Water, *Lancet* **2** 739-781, 1946.

may damage the vital function of the cells of the lower nephron by exposing them to high concentrations of hemoglobin, unattainable in the proximal nephron. While small amounts of protein are apparently constantly passing through the glomerulus and being reabsorbed, larger quantities are alien to the vertebrate tubule.²⁰ The persistence of some forms of proteinuria is eventually associated with renal tubular destruction, as observed with Bence Jones proteosuria, as well as with the excretion of certain globulins.²¹

Studies of renal impairment accompanying multiple myeloma carried out by one of us (R M S) have disclosed renal insufficiency in all cases in which the serum globulin exceeded 10 Gm per hundred cubic centimeters. A recent report of a case of renal insufficiency associated with Boeck's sarcoid²² similarly revealed elevation of the serum globulin level. This problem is still under investigation.

It is our view that the proteins hemoglobin and myoglobin in high concentration are toxic to the lower nephron, they or their degradation products are injurious to the distal tubular segment because hypertonic concentration resides in this renal region. Vasoconstriction and diminished renal blood flow produce tubular anoxia and increase tubular susceptibility to such injury.

An exhaustive and stimulating study of lower nephron nephrosis by Lucké²³ considers this among other possibilities. At the present time there is no cogent evidence which indicates that alkaline therapy is useful once hemolysis has occurred. Indeed fatal reactions have occurred in the presence of persistently alkaline urine.

The manner in which the patient described here died, in left ventricular failure, suggests a cardiac as well as a renal element as the cause of death. The terminal oliguria frequently observed in cases of mismatched transfusion and crush injury was lacking. It is thought that the immediate cause of death may have been the high level of potassium produced by the antacidosis regimen of potassium bicarbonate instituted because of the concomitant presence of heart failure, during

20 Dock, W. Proteinuria and Associated Renal Changes (Evans Lecture), *New England J Med* **227** 633-636, 1942. Ekehorn, G. Principles of Renal Function, *Acta med Scandinav*, 1931, supp 36, pp 1-717. Bott, P A, and Richards, A N. The Passage of Protein Molecules Through the Glomerular Membranes, *J Biol Chem* **141** 291-310, 1941.

21 Blackman, S S, Jr, and Davis, B D. Electrophoretic and Chemical Analysis of Protein in Nephritic Urine, *J Clin Investigation* **22** 545-549, 1943.

22 Klinefelter, H F, Jr, and Salley, S M. Sarcoidosis Simulating Glomerulonephritis, *Bull Johns Hopkins Hosp* **79** 333-341, 1946.

23 Lucke, B L. Lower Nephron Nephrosis (Renal Lesions of Crush Syndrome, of Burns, Transfusions, and Other Conditions Affecting Lower Segments of Nephrons), *Mil Surgeon* **99** 371-396, 1946.

which sodium ion is ordinarily withheld. This induced rise in serum potassium level paralleled the increase ordinarily seen in fatal cases of crush injury in which death is usually due to cardiac impairment with evidences of potassium poisoning resulting in the high T waves and the conduction disturbances observed in the electrocardiogram. The disturbance in ventricular conduction observed in the electrocardiogram of this patient may well have been due to hyperpotassemia. The frequent use of neostigmine may also have exercised a potassium effect on the cardiac muscle because of the rise in the local potassium level following the administration of cholinergic drugs.

The pathologic findings were interesting in that they revealed evidence of fresh and old tubular disease, with signs of an old inflammatory renal process as indicated by the thickening and adhesions of the

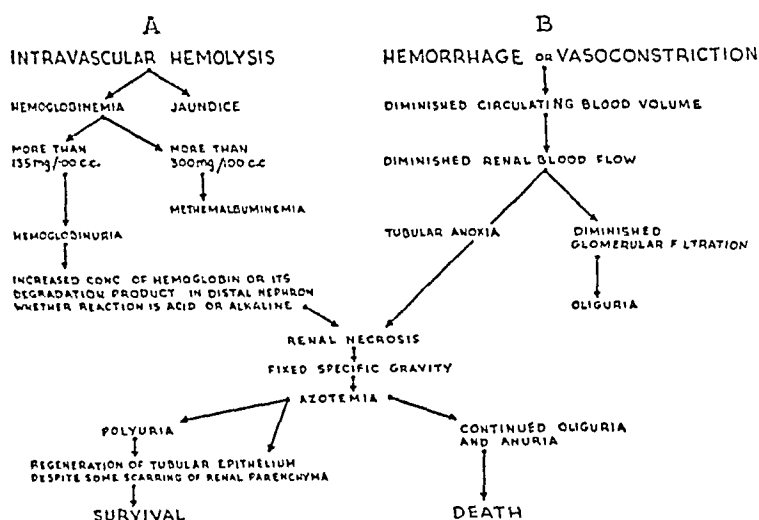


Fig 3—Scheme illustrating the mechanism of renal injury accompanying most cases of intravascular hemolysis. Note that renal necrosis is a result of varying combinations of factors *A* and *B*, that polyuria usually heralds improvement and continued oliguria or anuria indicates a fatal outcome and that acidification or alkalinization is not crucial to hemoglobin precipitation and tubular injury.

capsule, a diffuse fibrotic process with numerous scars and mononuclear infiltrates. The last were apparently remnants of renal injury resulting from eleven previous hemolytic episodes. It should be noted that no vascular changes were reported to suggest a vascular cause for the renal lesions.

The anatomic evidence thus supports the notion that progressive renal injury with final functional impairment results from repeated hemolytic episodes and that although tubular regeneration may be adequate to prevent renal decompensation in the initial attacks the destructive process finally damages so much renal tissue that there can be no return to adequate function. The same view may be applied to other forms of renal necrosis.

It is suggested that the patient's sudden death in left ventricular failure was related to the retention of serum potassium in the presence of renal insufficiency resulting from repeated intravascular hemolyses due to cold exposure

SUMMARY

1 A fatal case of renal tubular necrosis resulting from twelve attacks of paroxysmal cold hemoglobinuria is presented

2 The anatomic observations reflected old and recent renal injury apparently due to hemolytic episodes

3 The use of potassium salts for alkalization is thought to be responsible for the mode of death

4 The mechanism of renal necrosis accompanying paroxysmal cold hemoglobinuria, mismatched transfusion and crush injury is viewed as a result of tubular anoxia secondary to diminished circulating blood volume and toxic damage of the epithelium of the lower nephron by excessive concentrations of the globin proteins or their degradation products during hypertonic concentration of the urine

5 Repeated single hemolytic episodes associated with hemoglobinuria may each occasion quanta of renal damage which eventuate in significant and finally fatal impairment of renal function

JARISCH-HERXHEIMER REACTION IN NEUROSYPHILIS TREATED WITH PENICILLIN

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IN NEUROSYPHILIS an early reaction to the administration of spirocheticidal drugs (the Jarisch-Herxheimer reaction) may take one or both of two forms a transient rise in temperature during the first twenty-four hours after administration of the drug or an exacerbation of mental symptoms or neurologic signs during the first few days

Febrile reactions have been observed after the administration of arsenical drugs, bismuth and, more recently, penicillin The literature contains only brief comments concerning the incidence and severity of fever after the use of these drugs

Symptomatic Herxheimer reactions occur not only after the administration of spirocheticidal drugs but also during fever therapy (especially induced malaria) The variety of manifestations observed is related to the type of neurosyphilis For example, in patients with dementia paralytica there may occasionally occur exacerbations of the existing psychoses or the development of new symptoms Confusion, agitation, hallucinations and convulsions may sometimes develop In persons with tabes dorsalis lightning pains and urinary difficulties may be temporarily intensified during treatment or may appear for the first time The initiation of treatment has been reported to precipitate agitation or confusion even in patients with asymptomatic neurosyphilis

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This paper presents data concerning the Herxheimer reaction in patients with neurosyphilis given penicillin therapy. Febrile and symptomatic reactions to penicillin may occur during the treatment of both early and late syphilis, including most types of neurosyphilis. Such reactions have not been reported during the use of penicillin for other infections involving the nervous system or for a wide variety of acute systemic infections. Neither have they been observed after administration of procaine penicillin G (100 to 500 units per kilogram) to 40 male and female patients with gonorrhea¹. In this group, rectal temperatures were recorded at hourly intervals for twenty-four hours.

The present study is based on an investigation of 349 afebrile patients with neurosyphilis who were treated with aqueous penicillin alone at the Johns Hopkins Hospital between 1944 and 1948. Initial doses of penicillin ranging from 30,000 to 300,000 Oxford units were administered intramuscularly within the first six hours. Rectal temperatures were recorded every two to four hours. A febrile reaction was arbitrarily defined as a rise in temperature above 100 F (37.8 C). We are here concerned primarily with the febrile response and only secondarily with symptomatic reactions. No attempt is made to compare Herxheimer reactions observed during penicillin therapy with those observed during other methods of treatment.

RESULTS

1 *Incidence of Febrile Reactions*—Febrile reactions have been previously reported in 13 to 54 per cent of adult patients treated for various types of neurosyphilis with commercial penicillin². In the present series of 349 patients the total incidence was 34 per cent (table 1). Fever occurred after administration of commercial penicillin in 35 per cent (76 of 216 patients) and after administration of crystalline penicillin G³ in 32 per cent (43 of 133 patients). Since

1 Unpublished data

2 (a) Stokes, J. H., Sternberg, T. W., Schwartz, H., Mahoney, J. F., Moore, J. E., and Wood, W. B., Jr. The Action of Penicillin in Late Syphilis, *J. A. M. A.* **126** 73-79 (Sept. 9) 1944. (b) Koteen, H., Doty, E. J., Webster, B., and McDermott, W. Penicillin Therapy in Neurosyphilis, *Am. J. Syph., Gonorr. & Ven. Dis.* **31** 1-13 (Jan.) 1947. (c) Callaway, J. L., Noojin, R. O., Flower, A. H., Jr., Kuhn, B. H., and Riley, K. A. The Use of Penicillin in the Treatment of Syphilis of the Central Nervous System, *ibid.* **30** 100-124 (March) 1946. (d) Tucker, H. A., and Robinson, R. C. V. Neurosyphilitic Patients Treated with Penicillin. Probable Herxheimer Reactions, *J. A. M. A.* **132** 281-283 (Oct. 5) 1946. (e) Moore, J. E. Penicillin in Syphilis, Springfield, Ill., Charles C. Thomas, Publisher, 1947.

3 The crystalline penicillin G used in these studies was supplied by the Commercial Solvents Company, lot numbers 46042605 and 46082605. The potency was 1,500 to 1,540 units per milligram.

incidence was not related to the type of penicillin, the two groups are combined in all analyses except those relating to dosage

No significant race or sex differences in the incidence of reactions were demonstrated (table 1)

2 Incidence of Symptomatic Reactions—The number of patients with early symptomatic reactions in previously reported series has varied from 8 to 11 per cent of those treated⁴ Among the 349 persons in this series significant aggravations of mental symptoms or neurologic signs during the first one to six days of treatment occurred in only 6 (1.7 per cent) Two of these patients have been previously reported on^{2d} The symptoms or signs observed in the 6 patients were convulsions in 2 instances, confusion and disorientation in 2, hallucinations and delusions in 1 and signs of meningeal irritation in 1 All patients had associated febrile reactions In 4 patients the original diag-

TABLE 1—*The Relationship of the Incidence of Febrile Reactions After Administration of Penicillin to the Race and Sex of Patients with Neurosyphilis*

	Number Treated	Febrile Reactions	
		Number	Percentage
Race			
White	115	35	30
Negro	234	84	36
Sex			
Male	235	82	35
Female	114	37	32
Total	349	119	34

nosis was dementia paralytica (an incidence of 7.3 per cent for this diagnostic group) and in 2 asymptomatic neurosyphilis (1.4 per cent) No reactions were noted in patients with other forms of neurosyphilis However, it is possible that exacerbations of such complaints as lightning pains may not have been recorded The 2 patients with asymptomatic neurosyphilis and 1 of those with dementia paralytica had only transient symptoms, with no recurrence during the next two to three years The other 3 patients, who had been recognized as having advanced dementia paralytica before treatment was commenced, were committed to mental institutions One of these showed sufficient improvement to allow discharge from the hospital after three months The other 2 required custodial care for periods of nine and thirty months respectively

4 Gammon, G. D., Stokes, J. H., Steiger, H. P., Steele, W. H., Beerman, H., Ingraham, N. R., Jr., Gyorgy, P., Rose, E., and Lentz, J. W. Penicillin Therapy Alone in Neurosyphilis. An Analysis of Clinical Results, *Ann Int Med* 25: 412-432 (Sept.) 1946. Stokes and others^{2a} Callaway and others^{2c}

TABLE 2—*The Relationship of the Incidence of Febrile Reactions to the Stage and Type of Neurosyphilis*

Diagnostic Type	Stage	Number Treated	Febrile Reactions	
			Number	Percentage
Acute syphilitic meningitis	Early	17	4	24
Asymptomatic	Early and late	136	33	24
Meningovascular	Early and late	78	28	36
Dementia paralytica and dementia paralytica with tabes	Late	55	41	74
Tabes dorsalis, with or without primary optic atrophy	Late	40	9	23
Other types	Late	23	4	17
Total		349	119	34

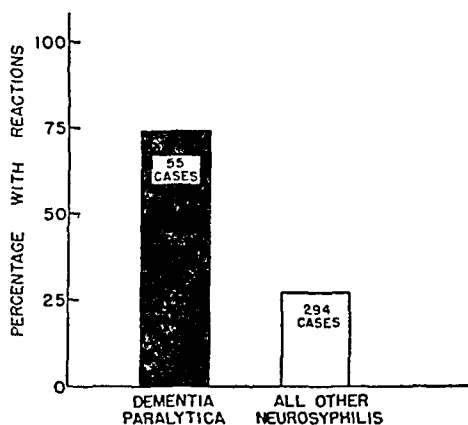


Fig 1—Relationship of the incidence of early febrile reactions to the diagnostic type of neurosyphilis

3 *Relationship to the Duration of Syphilitic Infection and to the Diagnostic Type of Neurosyphilis*—In contrast with the low incidence of febrile reactions to penicillin reported for most forms of neurosyphilis, a higher incidence of 64 to 79 per cent has been reported for dementia paralytica⁵ The present series, which includes 41 cases of dementia paralytica previously reported from this clinic,^{5a} amplifies this observation

The occurrence of febrile reactions according to the stage and type of neurosyphilis is presented in table 2 and figure 1. There is no relationship between incidence and duration of infection. In all types of neurosyphilis except dementia paralytica febrile reactions occurred in 17 to 36 per cent of the cases. However, in patients with dementia

5 (a) Reynolds, F W, Mohr, C F, and Moore, J E. Penicillin in the Treatment of Neurosyphilis. II Dementia Paralytica, J A M A **131** 1255-1260 (Aug 17) 1946. (b) Callaway and others^{2c}

TABLE 3—*Relationship of the Incidence of Febrile Reactions to the Abnormalities of the White Blood Cell Count and the Protein Content of the Cerebrospinal Fluid*

White Blood Cell Count and Protein Content	Dementia Paralytica			Other Types of Neurosyphilis			Total		
	No of Cases	Febrile Reactions		No of Cases	Febrile Reactions		No of Cases	Febrile Reactions	
		No	%		No	%		No	%
Both normal	7	1	14	46	5	10	53	6	11
Cells or protein increased	17	11	64	87	17	19	104	28	26
Both increased	31	29	93	161	56	34	192	85	44

paralytica a definitely increased incidence was observed. Febrile reactions occurred in 41 (74 per cent) of 55 patients with this type.

4 *Relationship to Abnormalities of the Cerebrospinal Fluid*—The incidence of febrile reactions was studied in relation to the white blood

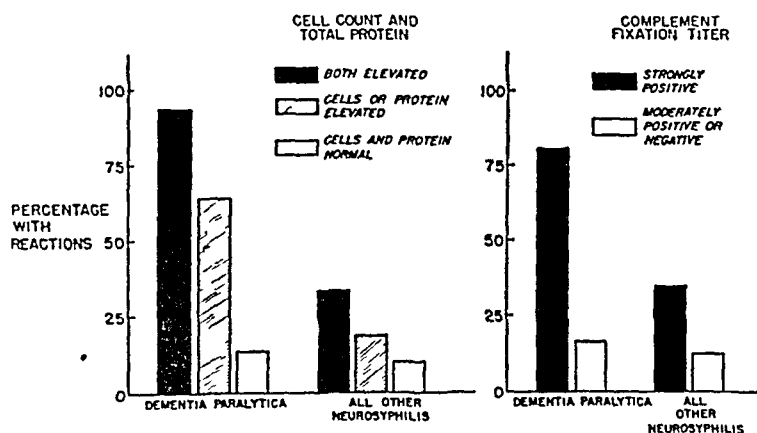


Fig 2—Relationship of the incidence of febrile reactions to the abnormalities in the cerebrospinal fluid

cell count and the total protein content, and also to the titer of reaction in the complement fixation test of the fluid. For the purpose of this study, we have arbitrarily regarded a white blood cell count of 10 or more or a protein content of 40 mg or more per hundred cubic centimeters as abnormal. Complement fixation titers of 0.2 to 1.0 cc have been defined as indicative of moderately positive reactions and those of 0.01 to 0.1 cc as indicative of strongly positive reactions.

The results presented in table 3 and figure 2 show that the frequency of reactions increased directly with increases in white blood cell count and total protein irrespective of the titer of the complement fixation test. This increase was more notable in patients with dementia paralytica but was also seen to a lesser extent in patients with other types of neurosyphilis. The highest incidence (93 per cent) was observed in patients who had dementia paralytica and in whom both the cell count and the protein content were abnormal.

When incidence was related to the titer of the reaction in the complement fixation test, to the exclusion of increased white blood cell counts and protein contents, it was observed that the more strongly positive was the reaction to the test the more frequent were febrile reactions. This was true for all types of neurosyphilis, but especially for dementia paralytica (table 4 and fig 2)

Table 5 further illustrates these relationships

TABLE 4—*Relationship of the Incidence of Febrile Reactions to the Complement Fixation Titer of the Cerebrospinal Fluid*

Reaction to Complement Fixation Test	Dementia Paralytica			Other Neurosyphills			Total		
	No of Cases	Febrile Reactions		No of Cases	Febrile Reactions		No of Cases	Febrile Reactions	
		No	%		No	%		No	%
Negative or moderately positive	6	1	16	114	15	13	120	16	13
Strongly positive	49	40	81	180	63	35	229	103	42

TABLE 5—*Relationship of the Incidence of Febrile Reactions to Abnormalities of the Cerebrospinal Fluid*

Cerebrospinal Fluid		Dementia Paralytica			Other Types of Neurosyphills			Total		
Reaction to Complement Fixation Test	White Blood Cell Count and Protein Content	No of Cases	Febrile Reactions		No of Cases	Febrile Reactions		No of Cases	Febrile Reactions	
			No	%		No	%		No	%
Negative Moderately positive	Both normal	0	0	0	10	1	10	10	1	10
	Both normal	2	0	0	32	3	9	34	3	9
	Cells or protein increased	3	0	0	43	6	14	46	6	13
	Both increased	1	1		29	5	17	30	6	20
Strongly positive	Both normal	5	1	20	4	1	25	9	2	22
	Cells or protein increased	14	11	79	44	11	25	58	22	38
	Both increased	30	28	93	132	51	39	162	79	49
Total		55	41	74	294	78	27	349	119	34

5 *Relationship to Serologic Tests for Syphilis*—There was no correlation of the incidence of febrile reactions with serologic negativity or with the height of the serologic titer

6 *Relationship to Previous Treatment*—Among 107 patients never previously treated, febrile reactions occurred in 41 (37 per cent). Of 87 patients who had received metal chemotherapy within a year of the administration of penicillin, 28 (32 per cent) had reactions. Of 14 patients in whom therapeutic malaria had been induced from two months to several years before administration of penicillin, only 1 had a

febrile reaction Of 9 patients who had received previous courses of penicillin, 2 had reactions

7 *Relationship to Dosage*—Febrile reactions have been observed after administration of as little as 1,000 Oxford units of penicillin⁶ In order to obtain detailed information concerning the incidence of reactions in patients with neurosyphilis in relation to the size of the initial dose, 202 patients treated with varying doses of crystalline penicillin G were studied The initial doses administered intramuscularly varied from 10 to 20,000 Oxford units of penicillin per kilogram of body weight (table 6) In each of these dosage groups the percentage of patients with decidedly abnormal cerebrospinal fluid and/or dementia paralytica was approximately the same

The incidence of febrile reactions after varying doses of penicillin (20 to 20,000 Oxford units per kilogram) ranged from 25 to 32 per

TABLE 6—*The Relationship of the Incidence of Febrile Reactions to the Dosage of Crystalline Penicillin G Administered to 202 Patients with Neurosyphilis*

Penicillin Dosage Given in First Six Hours		Patients Treated	Febrile Reactions	
Mg /Kg	Units/Kg		Number	Percentage
13.3	20,000 *	8	2	25
1.67 to 3.33	2,500 to 5,000 †	133	43	32
0.013 to 0.027	20 to 40 *	47	12	26
0.007	10 *	14	0	0

* Single dose only in first forty eight hours

† Therapeutic doses repeated every three hours

cent, with no definite trend in relation to dosage However, when doses of penicillin as small as 10 Oxford units per kilogram were given, reactions were no longer observed One of us has shown⁷ that the minimal dose producing a reaction in patients with early syphilis (10 units per kilogram) is approximately the same as that required to produce a reaction in patients with neurosyphilis

8 *Pattern of Fever*—The pattern of the febrile response in neurosyphilis was studied among the 119 patients with reactions The average temperature curve in this group is shown in figure 3, along with the curve previously observed in a study of patients with early syphilis⁷

In this group of patients with neurosyphilis the earliest elevation of temperature occurred four hours after the first injection In approximately 20 per cent the maximal elevations were recorded between six to

6 Olansky, S The Herxheimer Reactions of Relatively Small Doses of Penicillin, *Ven Dis Inform* 28:26-27 (Feb) 1947

7 Farmer, T W The Herxheimer Reaction in Early Syphilis Treated with Crystalline Penicillin G, *J A M A*, 158 480-485 (Oct 16) 1948

ten hours, in 50 per cent between twelve and sixteen hours and in 30 per cent between eighteen and twenty-four hours after injection. Thus, in the temperature curve for neurosyphilis there is an average rise to about 100 F (37.8 C) extending over a period of ten hours. Approximately 75 per cent of the patients had temperatures above this sixteen hours after the injection of penicillin. In the majority of instances the temperature remained above 100 F for four to ten hours. The individual elevations of temperature varied from 100.0 to 104.2 F.

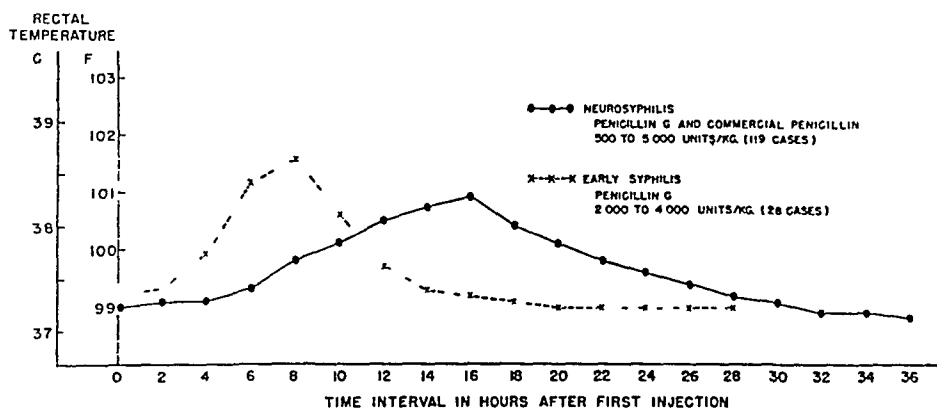


Fig 3—Average febrile reactions following the use of penicillin in neurosyphilis and in early syphilis

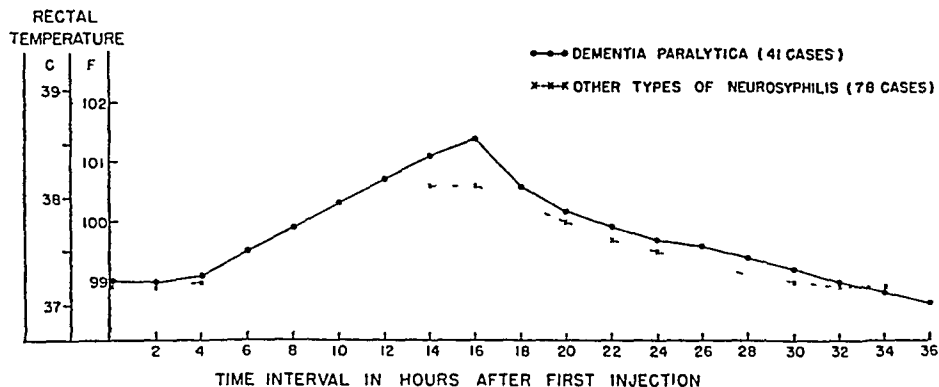


Fig 4—Average febrile reactions following the use of penicillin in dementia paralytica and in other types of neurosyphilis

(37.8 to 40.1 C), with an average of 100.9 F (38.3 C). All patients again had normal temperatures within thirty-six hours after the first injection.

The average febrile reaction to penicillin in patients with early syphilis, which reaches a maximum eight hours after injection and returns to normal by sixteen hours, is contrasted in figure 3 with the slower response in patients with neurosyphilis.

The temporal patterns of febrile response were similar in all the diagnostic types of neurosyphilis. The average temperature curve for

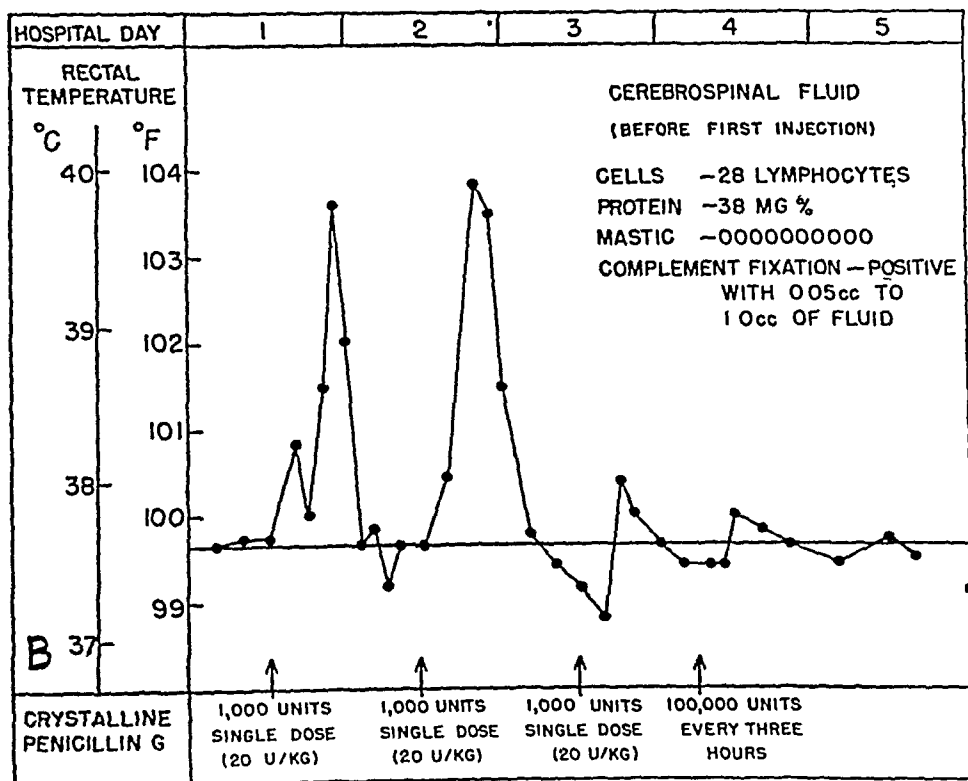
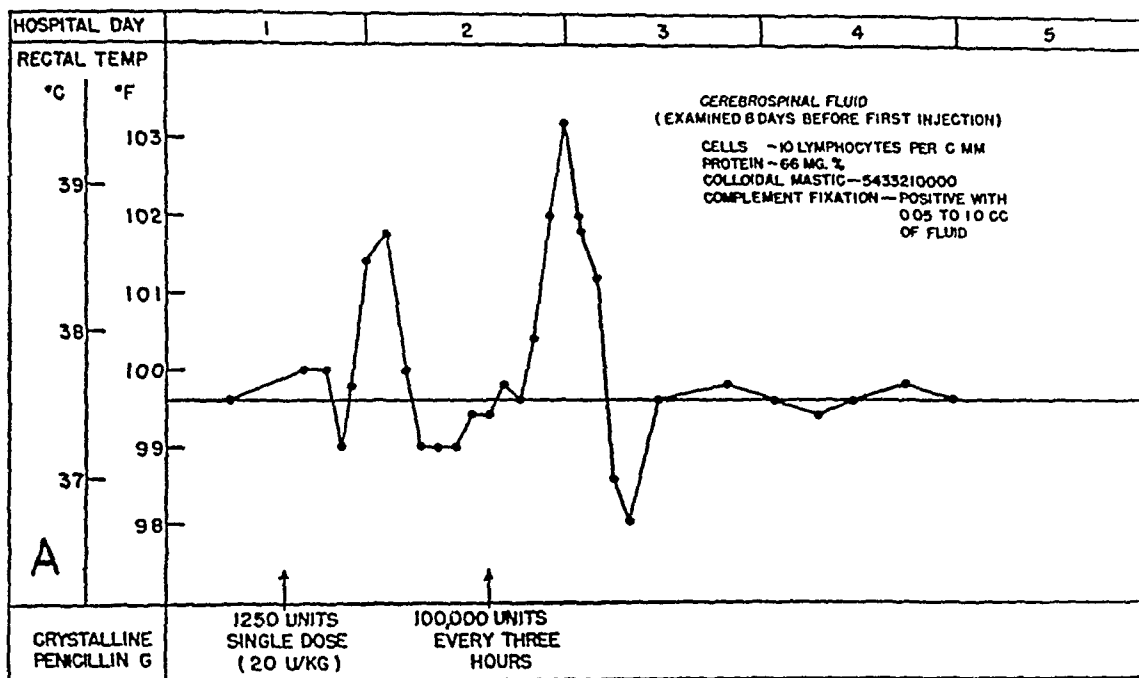


Fig. 5—A, double febrile reaction following the use of crystalline penicillin G in a patient with dementia paralytica, B, multiple febrile reactions following the use of crystalline penicillin G in a patient with late asymptomatic neurosyphilis

dementia paralytica is presented in figure 4 for comparison with that for other types of neurosyphilis. The maximal average temperature in each group was reached sixteen hours after injection. In patients with dementia paralytica this was 101.4 F (38.6 C) and in the remainder of the group 100.6 F (38.1 C).

The pattern of fever in 43 patients given usual therapeutic doses (2,500 to 5,000 units per kilogram) of crystalline penicillin G was approximately the same as that observed in 12 patients given small initial doses (20 to 40 units per kilogram). The earliest onset of fever was four hours after injection in each of the two groups. The individual maximum elevations of temperature were 103.2 F (39.6 C) and 103.8 F (39.9 C) in these two groups. The average maximal elevations were 101.0 F (38.3 C) and 101.2 F (38.4 C). This similarity in the pattern of fever in response to small doses and also to therapeutic doses of penicillin in the same patient is further illustrated in figure 5A.

9 Double Herxheimer Reactions—Of the 12 patients who had shown febrile reactions to small single doses of penicillin (table 6), fever again developed in 9 when they were given either a therapeutic dose or a repeated small dose of penicillin twenty-four to seventy-two hours later. This double Herxheimer reaction is illustrated in figure 5 and is essentially the same as that observed in cases of early infectious syphilis. Repetition of the febrile response was not observed after repeated large single doses of penicillin.

COMMENT

We have demonstrated that the Herxheimer phenomenon occurs in approximately one third of patients with neurosyphilis treated with penicillin. The incidence of this reaction is not related to the race or sex of the patient, to the duration of infection with syphilis, to the serologic titer of the blood or to the penicillin dosage (above a threshold level of 20 units per kilogram). However, it is definitely influenced by the diagnostic type of neurosyphilis and by the degree of abnormalities in the cerebrospinal fluid. Febrile reactions occur in three fourths of the cases of dementia paralytica but in only one fourth of the cases of other types of neurosyphilis. The occurrence of this reaction is related also indirectly to the increased white blood cell count and total protein content and to the degree of positivity of the complement fixation reaction in the cerebrospinal fluid. However, two observations suggest that the character and degree of the abnormalities of the fluid are by no means the sole influencing factors. First, among 17 patients with acute syphilitic meningitis and with pronounced abnormalities in the fluid only 4 had reactions. Second, among patients with early syphilis

the presence or absence of abnormalities in the cerebrospinal fluid before treatment did not affect the incidence of reactions⁸

The observations presented concerning two aspects of the febrile reaction in cases of neurosyphilis, *i. e.*, the incidence and the pattern of fever, are at variance with those made in cases of early syphilis. Thus, approximately one half of the patients with early infectious syphilis had fever in response to penicillin, and this incidence was not related to the stage of infection. In contrast with this, 93 per cent of a selected group of patients with dementia paralytica and markedly abnormal cerebrospinal fluid showed reactions. Also, individual responses in patients with neurosyphilis followed a much more irregular temporal pattern than those in patients with early syphilis.

In neurosyphilis, as in early syphilis, the reaction is an all or none phenomenon. It occurs with equal incidence and severity with any dose of penicillin above a threshold level (10 to 20 units per kilogram). This dose is too small to destroy surface organisms in lesions in early syphilis. The reaction cannot be avoided by administration of penicillin in this small initial dose. In patients with neurosyphilis, as in those with early syphilis, multiple febrile responses may be produced by repeated small doses but not by repeated large doses.

An elucidation of the mechanism of the Herxheimer reaction in early syphilis and in neurosyphilis will require the unraveling of these many variables. The present clinical observations on patients with neurosyphilis point to the need for additional study, particularly of patients with dementia paralytica.

SUMMARY

1 Febrile Herxheimer reactions were observed in 34 per cent of 349 patients with various types of neurosyphilis treated with penicillin. Seventy-four per cent of patients with dementia paralytica had reactions. The incidence was significantly higher in patients with increased white blood cell counts, increased total protein contents and strongly positive reactions to complement fixation tests of the cerebrospinal fluid than in patients who had a normal cell count and a normal protein content in the fluid.

2 The incidence of the reactions in patients recently treated with metal chemotherapy was similar to that observed in previously untreated patients.

3 The temporal patterns of the febrile reactions in patients with neurosyphilis were variable. Maximal responses occurred over the wide range of four to twenty-four hours after the injection of penicillin.

8 Unpublished data

Approximately 50 per cent of the patients had maximal elevations in temperature between twelve and sixteen hours after injection

4 The incidence of febrile reactions after small initial doses of penicillin (20 units per kilogram) was approximately the same as that observed after the usual therapeutic doses (2,500 to 5,000 units per kilogram) With an extremely small dose (10 units per kilogram) of penicillin, reactions were not observed

5 With repeated small doses of penicillin (20 units per kilogram), double and multiple reactions were produced in the same patients

6 These observations demonstrate that febrile reactions in patients with neurosyphilis are not prevented by the administration of small initial doses of penicillin in the range of 20 units per kilogram of body weight

News and Comment

GENERAL NEWS

United States Army Dedicates New Hospital—Army officials announce the dedication of Tripler General Hospital, latest and finest addition to the medical facilities of the United States Army, at a formal ceremony held at the hospital on Moanalua Ridge, Honolulu, Hawaii, on Sept. 10, 1948

The dedication day program, to which the public was invited, included an "open house" tour of the 1,500 bed structure. The ceremony was held in the hospital's flagpole area, which commands a sweeping view of Honolulu's ocean front from Diamond Head to Pearl Harbor and beyond. Here prominent civil and military officials gathered, with representatives of Hawaii's business and community life, formally to dedicate the hospital structure, which will afford vitally needed military facilities for adequate care of sick and convalescent patients under treatment in the Middle Pacific areas.

This Army hospital, which is capable of expansion in a critical emergency, normally will provide care for United States Army and Air Force personnel and their dependents, patients assigned by the Veterans Administration and patients submitted for entrance by the United States Public Health Service.

Tripler, which replaces the 147th General Hospital, long familiar to Honoluluans as "Old Tripler," opposite Fort Shafter on King Street, is an Army post under command of Col. H. H. Twitchell, Medical Corps. The main hospital unit is a miniature city in itself, having, in addition to its comprehensive medical facilities, wards, dining rooms, kitchens, supply rooms, engineering plant and administrative offices, such other features as a radio station, post office, libraries, barber and beauty shops and post exchange.

In addition to the main hospital buildings, Tripler General Hospital includes nurses' quarters, enlisted men's barracks and mess, motor pool, warehouse and commissary, fire house, incinerator, gate house, utility shops, laundry and boiler house.

Work is authorized for the construction in the near future of a patients' recreation building, a gymnasium, athletic field, tennis courts and additional housing, for personnel.

When completed, the hospital grounds will be landscaped as a great garden of tropical trees and shrubs, making Tripler General Hospital not only a medical asset of vast proportions to Hawaii, but also an attraction of scenic beauty.

National Gastroenterological Association Announces Its 1949 Award Contest—The National Gastroenterological Association announces its annual cash prize award contest for 1949. One hundred dollars and a certificate of merit will be given for the best unpublished contribution on gastroenterology or allied subjects. Certificates will also be awarded those physicians whose contributions are deemed worthy.

Contestants residing in the United States must be members of the American Medical Association. Those residing in foreign countries must be members of a similar organization in their own country. The winning contribution will be

selected by a board of impartial judges, and the award is to be made at the annual convention banquet of the National Gastroenterological Association in October 1949

Certificates awarded to other physicians will be mailed to them. The decision of the judges will be final. The association reserves the exclusive right of publishing the winning contribution, and those receiving certificates of merit, in its official publication, *The Review of Gastroenterology*

All entries for the 1949 prize should be limited to 5,000 words, typewritten in English, prepared in manuscript form, submitted in five copies and accompanied with an entry letter. They must be received not later than April 1, 1949. Entries should be addressed to the National Gastroenterological Association, 1819 Broadway, New York 23

International Congress on Rheumatic Diseases Announced—The first International Congress on Rheumatic Diseases to be held in the United States will meet at the Waldorf Astoria in New York May 30 to June 3, 1949

Seven scientific sessions are planned, as well as five one hour round table conferences on various clinical topics, under the leadership of authorities in the respective fields. Short clinics, papers and reports will be given concurrently at four or five New York hospitals during the three afternoons

Instantaneous translations of the scientific papers will be made by means of the I B M wireless system. The official languages of the congress will be English, French and Spanish

The meeting will be an open one. Members of the International, the European and the Pan American Leagues against Rheumatism, as well as the Canadian Rheumatism Association, the British Empire Rheumatism Council, the Heberden Society of London and the ten state or city rheumatism societies affiliated with the American Rheumatism Association are especially invited

PERSONAL NEWS

Dr A J Carlson Given Honor Award of Mississippi Valley Medical Society—Dr A J Carlson, of Chicago, has received the Honor Award of the Mississippi Valley Medical Society for 1948, a gold medal and a certificate

The "Honor Award" is a new award given by the society from time to time to those who have made distinguished contributions to clinical medicine. Dr Carlson is the first recipient. He is the Frank P Hixon Distinguished Service Professor Emeritus of Physiology at the University of Chicago and past president of the American Biological Society, the American Physiological Society, the American Association for the Advancement of Science, the American Association of University Professors, the Federation of American Societies for Experimental Biology and the Institute of Medicine of Chicago. He has long been known for his medical school teaching (since 1904), his research work and his contributions, which exceed 200 articles and books, in the fields of physiology and nutrition

Dr Louis H Jorstad Given Distinguished Service Award of Mississippi Valley Medical Society—Dr Louis H Jorstad, of St Louis, has been honored by the Mississippi Valley Medical Society as the recipient of its Distinguished Service Award for 1948. The award consisted of a gold medal and a certificate

Dr Jorstad has given much of his time to postgraduate medical education and has served with distinction on the staffs of a number of well known St Louis hospitals. For the past ten years he has been chairman of the Missouri State Chapter and the Greater St Louis Chapter of the American Cancer Society and also an officer in the Mississippi Valley Medical Society

Correspondence

PROTHROMBINOPENIC EFFECT OF PENICILLIN

To the Editor —Because of the war in our country we lost contact for a time with the recent American medical publications, and it has been only lately that we received the back numbers of the ARCHIVES OF INTERNAL MEDICINE

In the review on syphilis by F W Reynolds and J E Moore (ARCH INT MED 81 85 [Jan] 1948) the action of penicillin on prothrombin in blood is mentioned. The authors quote reports from literature showing thrombopenic, as well as thromboplastic, effects of penicillin, without concluding which of these results is the correct one, but they add that there is no report of thrombotic accidents in medical practice after use of penicillin.

In this connection I should like to direct your attention to the article "Prothrombinopenic Effect of Penicillin in Men" (Lewitus, Z A, and Aschireli, A Harefuah 35 15 [July 15] 1948) in which we showed that in 94 per cent of our patients who received penicillin there was a definite decrease of the prothrombin activity in the blood to a level between 50 and 60 per cent of normal. The depression lasted during the entire time of penicillin medication, the prothrombin returning after interruption of medication to the previous levels. This decrease in prothrombin could be corrected by injections of vitamin K. We thought this effect of penicillin to be analogous to the one known to occur from the sulfonamide drugs.

The contradictions of the investigators regarding the effect of penicillin on the prothrombin seem largely influenced by the fact that in the first hours after penicillin medication a rise in prothrombin activity sometimes occurs, and the prothrombinopenic effect becomes evident only after elapse of three to four days.

We saw the practical implications of these facts in the combined penicillin-dicumarol therapy for infective thrombotic processes, in which we had to use much less dicumarol than is usually prescribed.

Z A LEWITUS, M D, Affuleh, Israel

Book Reviews

Lipoidtransport Belyst ved studier over lipaemi i graviditet og laktationsperiode By Mogens Ingerslev Pp 107 Copenhagen Ejnar Munksgaards Forlag, 1942

This monograph concerns studies on blood lipids in the cat and rabbit, in non-pregnant, pregnant and lactating animals, in an attempt to elucidate the question concerning the transport of fatty acids across the cell membrane. The transport of lipid through the placental membrane is considered as a paradigm of lipid transport through cell membranes in general.

From experiments performed, no decisive role could be attributed to the effect of the estrogenic hormone, the corpus luteum or the chorionic hormone on blood lipids. Hyperlipemia in pregnancy is considered a physiologic expedient and hypolipemia as due to difficulty experienced by some animals in meeting the increased demands which pregnancy makes on the fat exchange. Varying blood levels during lactation are considered to be related to differing degrees of activity of the mammary tissue.

From experiments on pregnant animals, evidence indicates that an active transport of lipid material occurs through the placenta in the last part of gestation. Fatty acids are transported through the placenta largely as neutral fat, to a lesser degree as phospholipids and only in minor amounts as cholesterol esters. No information could be obtained of the amount or form in which fatty acids are transported from the blood stream to the mammary gland.

Approved Laboratory Technic By John A. Kolmer, M.D., Ph.D., Sc.D., LL.D., F.A.C.P., and Fred Boerner, M.D. Fourth edition Price, \$10 Pp 1,017 New York D. Appleton-Century Co., Inc., 1945

This textbook has enjoyed such general acceptance as an authority in its field for so many years that it is difficult for a reviewer to do more than call attention to a new edition.

As the editors point out, the present edition has been extensively revised and rewritten, in addition to which a considerable amount of new material has been added to encompass the newer methods for existing determinations where these represent an advantage in facility of performance and accuracy as well as a wealth of entirely new technics. The material is presented in a lucid manner, with an admirable degree of compromise between too little detail for the student and a burdensome amount for the expert. This text is confined in the main to technical procedures and normal values, the changes due to disease and their interpretation being considered in a separate book by Dr. Kolmer.

This has been found a useful reference work both in the laboratory and for teaching purposes.

Nuove vedute sulla malaria By M. Ascoli, M.D. Pp 211 Rome Istituto Bibliografico Italiano, 1945

This book is a collection of a series of lectures on malariology held at the University of Palermo in 1945 by Professor Ascoli and his associates.

Since 1936 Professor Ascoli has written widely on his concept of the malaria infection as a two phase process: a first (septicemic) phase, responsible for the acute episodes of the disease in which the parasites circulate and reproduce in

the blood stream, and a second (focal) phase, in which the parasites perpetuate the infection by remaining in the red blood cells stationed in the ordinary blood reservoir organs (especially the spleen). This situation would be responsible for the occurrence of relapses and for the bad condition of the patient between acute episodes. The first phase responds to chemotherapy, the second does not. However, intravenous injection of increasing amounts of epinephrine hydrochloride, from 1/100 to 1/10 mg, over a variable period (twenty to thirty days) exercises an important therapeutic action in the focal phase by preventing, to a large extent, further relapses and improving the general state of the patient. The mechanism of this therapeutic effect is probably mainly connected with the splenocontraction determined by the epinephrine as well as other factors, obscure at present.

The physiologic basis, clinical results, modifications induced in some biochemical findings and technic of the hormonal therapy are presented in the first part of the book. Of particular interest are new statistical data offered to show the drastic reduction in the number of relapses after hormonal therapy and its effect in extremely serious cases of pernicious malaria and other severe complications when administered in very high doses (1/10 Gm twice a day) and when associated with quinine given parenterally. The second part of the book includes a heterogeneous series of lectures covering problems of epidemiology and transmission of the malarial infection. The possibility of the existence of an extra-erythrocytic cycle of the malarial parasite (as suggested by Raffeale) is discussed with relation to its importance in the understanding of the malarial infection. Also of interest is a chapter showing ineffectual results in securing eradication of the disease at the chronic stage through protracted chemotherapy in the out seasonal period.

The book is intended principally to give current information to the general practitioner practicing in malarial areas. As such, it is of profitable and interesting reading. To the more experienced worker, however, the main interest of the book is in the well documented discussion of the epinephrine treatment of malaria which has received much undeserved criticism even in the country in which it was devised. From this point of view, the book is stimulating and useful for consultation.

Cardiopatas congenitas de la infancia By Agustín Castellanos y Gonzalez, M.D. Price, \$9. Pp 406, with 59 illustrations. Habana: M. V. Fresneda, Publisher, 1947.

This work constitutes a textbook for a course on congenital heart disease given by the author at the University of Habana. It is primarily aimed, however, at the pediatrician rather than at the student, as the material is covered in a fairly exhaustive manner. The embryologic basis of cardiac anomalies is well reviewed, followed by a discussion of the methods of the investigation that apply to congenital heart disease. A discussion on cyanosis, including gasometric studies, is then presented and followed by a general description of the cyanotic syndromes. Detailed studies of the individual congenital cardiac abnormalities constitute the final section of the book.

Emphasis is primarily laid on diagnosis, prognosis and treatment, and particular attention is given to those congenital cardiac conditions that are amenable to surgical correction. Particularly impressive are the descriptions of roentgenographic and gasometric studies as they apply to the definitive diagnosis of cardiac anomalies. Many diagrams and a number of photographic reproductions

of angiograms are included for purposes of illustration of the diagnostic features involved

This book is of great interest to anyone who desires to obtain information on cardioangiographic technics and interpretation, and having been one of the earliest workers in this particular field, Dr Castellanos is well equipped to supply it. Many of the angiographic concepts discussed represent the author's original work, but abundant references are made to other investigators.

Kinesiology Handbook, A Study Guide and Laboratory Manual By Gladys Scott, State University of Iowa Price, \$2 Pp 148 New York F S Crofts Company, 1947

As has been pointed out by Dr C H McCloy in the introduction to this handbook, "the concepts of mechanics have usually been taught with no relationship to the movements of man." The author has overcome this difficulty by assembling special experiments and problems which do apply to man. This text is "designed as a workbook and study aid for students of kinesiology." It includes twenty-one lessons on various phases of kinesiology, and in each lesson there is an introduction, a list of references, a list of equipment required for the lesson, a description of the project and finally a list of questions elucidating the facts learned from the lesson.

Such subjects as motion in relation to structure of joints, action of the muscles of the various parts of the body, muscular tonus, muscular fatigue, leverage, inertia, relaxation, locomotor skills, development of muscular strength and of muscular tonus and measurement of strength of groups of muscles are discussed. Professors of anatomy in our medical schools might well advocate greater consideration of this subject in teaching medical students because modern physicians should be well grounded in kinesiology and functional anatomy.

This handbook is well organized and well planned and should prove a useful teaching aid, not only for students of physical education, physical therapy and occupational therapy but also for medical students.

Psychobiology and Psychiatry A Textbook of Normal and Abnormal Human Behavior By Wendell Muncie, M D Second edition Price, \$9 Pp 620 St Louis The C V Mosby Company, 1948

The second edition of this book is disappointing in many ways, most particularly because it falls short of its purpose, which is to present an eclectic approach to and an explanation of the problems of psychiatry. Even so, it is the most complete textbook statement of the many important contributions made to psychiatry by Dr Adolf Meyer and his students. The disappointments arise from omissions, condensations, misplaced emphasis and elaboration of details tangential to the truly pertinent data of psychiatry.

The contents constitute three rather distinct monographs. Part I, "Psychobiology—The Study of Normal Behavior," is presented in four chapters. It contains an outline of the Meyerian assessment of personality, and it is essentially a descriptive and an evaluative analysis of behavioristic phenomena. As an outline of a clinical inquiry into the resources of the total human personality, its growth, development and maturation, it is necessarily abbreviated and condensed. Although it subsumes the nodal points of a comprehensive discussion, it lacks the requisite definition for a student's textbook.

Part II, "Abnormal Behavior—Pathology and Psychiatry," in 14 chapters treats of the gamut of disorders which comprise the typical deviations from modal

behavior These are organized in a form which covers the classic clinical features of each syndrome They are illustrated by case presentations with graphic life charts including the therapeutic regimen which has been followed and contain a summary of comments

Part III, "Treatment," consists of all chapters which describe the essentials of psychiatric treatment in a general fashion Mention also is made of the specific technics which are useful in the management of the syndromes discussed in part II However, the presentation in this part has been sacrificed to the first two parts For example, insulin and electroshock therapy have been slighted The discussion of prefrontal leukotomy is similarly condensed The details of narcosis and use of barbiturates for interviews are sketchy Too casual mention is made of the problems of alcoholism and drug addiction The therapy for states of vitamin deficiency is superficial

A disproportionate emphasis is given to the minutiae of examination The orientation of medical students in the principles of dynamic psychiatry requires that they know more than the way in which to elicit or record descriptions of ideation, affect or behavior The pages which are devoted to the superfluous outline of neurologic reflexology and to unelaborated listing of general, not particularly informative statements about the physical concomitants of mental disease could well have been used for this purpose

On the other hand, the sections which are given to clinically descriptive psychiatry are complete for students' purposes Each nosologic category is illustrated by a well chosen case study If the author had synthesized and integrated the wealth of material he presents and related it to a more dynamic developmental background, he would have accomplished the goal of an eclectic orientation

An Introduction to Gastro-Enterology By James Dunlop Lickley, M D
Price, \$3 Pp 143 Baltimore The Williams & Wilkins Company, 1947

This is an elementary manual intended for beginners who are interested in studying, in a resume form, the anatomy and physiology of the digestive tract It may prove of some assistance to physicians in their postgraduate courses The last 50 pages of the book deal with some practical clinical applications A correlation of physiologic facts with various signs and symptoms is made, but no attempt has been made to outline the treatment

Las arritmias en clínica (diagnóstico, pronóstico y tratamiento) By Antonio Battro, M D Pp 511, with 299 illustrations Paper Buenos Aires "El Ateneo," 1948

The title of this book does not do the work full justice While the author deals adequately with cardiac arrhythmias, their diagnosis and treatment, he prefaces this with a discussion of the heart beat from the physiologic standpoint

He deals well with the fundamentals of electrocardiography, including unipolar chest and limb leads, and other methods of registration, including heart sounds This is something that other writers in this field might well imitate He does not consider seriously electrocardiographic studies of conditions other than arrhythmias But this is not his intention

The discussion of arrhythmias covers well known forms and some less common ones such as the Wolff-Parkinson-White syndrome and ventricular fibrillation Included, of course, are the blocks, both auriculoventricular and bundle branch blocks There is also a short discussion of the use of esophageal leads

Illustrations and diagrams, particularly those dealing with physiologic aspects and the tracings obtained by means of unipolar electrocardiograms, are particularly good

One will find here an excellent discussion of all types of cardiac arrhythmias, together with an equally good bibliography in this field

Medical Research in War Report of the Medical Research Council for the Years 1939-45 by the Committee of Privy Council for Medical Research Price, 7s 6d (approximately \$1.75) Pp 455 London His Majesty's Stationery Office, 1948

This impressive report of the Medical Research Council for the years 1939 to 1945 is the counterpart of the American "Advance in Military Medicine" recently published under the sponsorship of the Committee on Medical Research. The British report is of particular interest for the record since it enumerates the names of all concerned as well as abstracts of the work accomplished. One is amazed at the extent and the scope of the ground covered—a real tribute to the contributions of civilians to military medicine.

Arterial Hypertension. A Follow-Up Study of One Thousand Hypertonics By Poul Bechgaard Price, 8 kroner Pp 358 Copenhagen Arnold Busck, 1946

This 350 page paper-bound volume comprises a clinical and statistical evaluation of over 1,000 cases of arterial hypertension. These cases were observed by the author in the outpatient department of the Poli Clinic of the Rigshospital in Copenhagen. Original hypertensive clinical and laboratory studies were made between 1931 and 1938 on all patients with blood pressures of 180 systolic or 160 systolic and 100 diastolic, and repeated examinations were made four to eleven years later.

Few prolonged and detailed studies have previously been made on a large series of hypertensive patients. This study was undertaken in order to help establish a base line for a clinical classification, predominant symptoms, complicating diseases, age groups and prognosis in relation to untreated patients with hypertension. Such a basis of comparison is necessary in order to evaluate both modern and future methods of therapy of hypertensive disease.

The author has generously summarized the outstanding American literature on hypertensive vascular disease as it has referred to etiologic factors, morbid classification, clinical evidence and causes of death. He has emphasized renal complications as they reveal themselves during the course of hypertension. His findings in this group of patients reveal that malignant nephrosclerosis occurs in approximately 1 per cent of all patients with hypertension.

As the cause of death, heart disease ranks first in 45 per cent of the patients, apoplexy second in 16 per cent of the patients and renal insufficiency third in 10 per cent of the patients. All in all, his investigation revealed a rather good prognosis for hypertension. In men the total mortality rate was found to be 288 per cent and in women 143 per cent when the mortality ratio of 100 per cent in the Danish population was used. The prognosis is particularly good in women who have noncomplicated hypertension with diastolic pressures below 130 mg. The mortality figures are only slightly higher than those for the general population.

Although these studies are not particularly revealing, they do represent a detailed piece of clinical investigation extending over a long period. The statistical material is well presented and is of interest to the student of hypertensive vascular disease.

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